Prevalence of diabetes and depression, and their association: a population-based study in Northeastern Brazil

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ACTH	Adrenocorticotropin Hormone
ADA	American Diabetes Association
AVP	Arginine Vasopressin
BF%	Body Fat Percentage
BMI	Body Mass Index
BRICS	Brazil, Russia, India, China and South Africa
BW	Birth Weight
CBG	Corticosteroid-Binding Globulin
CE	Ceará
CHOD-PAP	Cholesterol Oxidase - Phenol + Aminophenazone
CHW	Community Health Workers
CI	Confidence Interval
CVDs	Cardiovascular Diseases
CRH	Corticotropin-Releasing Hormone
CRP	C-Reactive Protein
DALYs	Disability-Adjusted Life Years
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complications Trial
DM	Diabetes Mellitus
DSM-III	Diagnostic and Statistical Manual of Mental Disorders - Third Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition
FPG	Fasting Plasma Glucose

GDM	Gestational Diabetes Mellitus
GDP	Gross Domestic Product
GPO-PAP	Glycerol-3-Phosphate Oxidase - Phenol + Aminophenazone
HbA1c	Glycated Haemoglobin
HDL-C	High-Density Lipoprotein Cholesterol
HDRS	Hamilton Depression Rating Scale
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal axis
IBGE	Brazilian Institute of Geography and Statistics
ICD-10	International Statistical Classification of Diseases and Related Health Problems - 10th Revision
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IPAQ	International Physical Activity Questionnaire
LDL-C	Low-Density Lipoprotein Cholesterol
LMICs	Low- and Middle-Income Countries
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MS	Metabolic Syndrome
MW	Minimum Wage
NDD	Newly Diagnosed Diabetes
NCDs	Non-Communicable Diseases

NGSP	National Glycohemoglobin Standardization Program
NGT	Normal Gucose Tolerance
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PCOS	Polycystic Ovary Syndrome
PPP	Purchasing Power Parity
PUFAs	Polyunsaturated Fatty Acids
SBP	Systolic Blood Pressure
SNS	Sympathetic Nervous System
SSRI	Selective Serotonin Reuptake Inhibitors
T2DM	Type 2 Diabetes Mellitus
TNF-α	Tumor Necrosis Factor α
VAMS	Visual Analogue Mood Scale
WHO	World Health Organization
WHR	Waist-to-Hip Ratio

ABSTRACT

Title: Prevalence of diabetes and depression, and their association: a population-based study in Northeastern Brazil.

Background: Diabetes and depression are common and rapidly increasing non-communicable diseases throughout the world. Currently, about 382 million people have diabetes worldwide, while depression affects approximately 350 million people. Some studies have found a frequent co-existence of depression, hyperglycemia, diabetes and diabetes-related complications. Moreover, comorbid depression in diabetes has been associated with poorer adherence to diabetes treatment regimens, increased risk of work loss and functional disability, increased mortality rates, higher health care costs, and decreased quality of life. Although the association between these two conditions has been found by several, the transcultural validity of these findings still needs to be demonstrated.

Objectives: The main objectives of the study were to investigate the prevalence of type 2 diabetes and depression, and the association between depressive symptoms and newly diagnosed diabetes in Northeastern Brazil. In addition, we wanted to investigate the agreement between two different types of depression scales: the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HDRS).

Methods: The prevalence of diabetes was assessed in the Northeast region of Brazil in a randomized population-based survey following the WHO criteria of 1999. Seven hundred and fourteen subjects participated in the study. Depression was assessed by MADRS and HDRS, before the diagnosis of diabetes was made known to the participants and investigators. Socio-demographic and economic information, as well as anthropometric measures were collected.

Results: A high prevalence of diabetes was found (Total 16%; Male 13.2% and Female 17.4%). Following MADRS, the rate of depression was 15% (Male 7% and Female 19.1%). According to HDRS, the rate of depression was 15.5% (Male 8.3% and female 19.3%). The agreement between MADRS and HDRS was found to be excellent (Kappa of 0.913, $p < 0.001$). Depression was the second strongest risk indicator for the occurrence of diabetes after controlling for potential confounding fators.

Conclusions: We found a high prevalence of both diabetes and depression in this population. Depression was a strong independent risk indicator for the occurrence of diabetes. An inverse significant association between diabetes and the risk for developing depressive symptoms

was also observed. The results may indicate that the treatment of depression should be included both for prevention and treatment of diabetes.

CHAPTER 1

INTRODUCTION

1.1 COUNTRY PROFILE

The Federative Republic of Brazil is by far the largest and most populous country in South America. Initially inhabited by indigenous people, Brazil was officially discovered by the Portuguese in 1500. After more than three centuries of Portuguese dominance, Brazil became an independent country in 1822, maintaining a monarchical system of government until 1889, when the monarchy was ousted and a republic established by the military. Throughout the next century, the country alternated between short periods of elected government and long periods of authoritarian rule. Finally in 1985, the ruling military dictatorship peacefully relinquished power, and today Brazil is a stable democracy (1).

A brief overview of the country will be provided in the following paragraphs.

1.1.1 Geography

Figure 1.1: Map of Brazil

Located in eastern South America along the Atlantic Ocean, Brazil is the fifth largest country in the world, and the third largest in the Americas. It shares borders with every country in South America, except for Ecuador and Chile. Brazil is officially divided into five regions (North, Northeast, Center-West, Southeast and South), and is composed of 26 states and 1 federal district, the capital, Brasília. Geographically diverse, Brazil has a wide range of weather conditions, topographies and natural resources (2, 3).

1.1.2 People and Demography

According to the Brazilian Institute of Geography and Statistics (IBGE), the population of Brazil was approximately 191 million in 2010 (unofficial sources have estimated that the population in 2014 surpassed 200 million), with a sex ratio of 0.95 male/female and about 84.3% of the total population living in urban areas. The Brazilians are mainly concentrated in the Southeastern (around 80 million inhabitants) and Northeastern (53 million inhabitants) regions, whereas the two largest regions, the Center-West and the North, that together constitute 64.1% of the total territory, have only 29.1 million people (4).

As a consequence of five centuries of miscegenation between European colonizers (mainly Portuguese), slaves from Africa, and autochthonous Amerindians, the Brazilians compose one of the most heterogeneous societies in the world. Despite criticism, IBGE classifies the different ethnic groups in Brazil according to the self-perception of the skin color. Thus, as reported by the 2010 Demographic Census, about 47.7% of the population described themselves as White, 43.1% as Brown (mixed white and black - *pardo* in Portuguese), 7.6% as Black, 1.1% as Yellow (Asian), and 0.4% as Amerindian (officially called *indígena*, that is indigenous). Although some minority languages are used throughout the country (Amerindian languages and other languages spoken by immigrants and their descendants), Brazil's official language is Portuguese, which is spoken by almost all Brazilians and is virtually the only one used in mass communication channels (3, 4).

The Brazilian demographic transition began in the mid-1950s. However, it was only during the past decades that it became an issue of greater interest. Recently, Brazil has experienced steady declines in fertility (total fertility rate in 1960 was 6.3 children born/woman, compared to 1.81 in 2013), substantial reductions in population growth rate (2.99% in the period 1950/1960, compared to 1.17% in 2000/2010), and an age pyramid weighted more towards adults and elderly (between 2002 and 2012, the population aged under 25 decreased from 47.4% to 39.6%, while the population group aged over 45 increased from 23% to 29%) (5, 6). Like in other capitalist countries, the Brazilian ongoing demographic transition has been directly related to the processes of industrialization and urbanization. The adoption of an agricultural production model, characterized by wealth concentration and low demand of labor force, had an important effect on the demographic dynamics, by continuously compelling agricultural workers to leave the countryside towards the cities. Additionally, the increases of per

capita income and education levels of the population have also been indicated as crucial elements to explain the Brazilian demographic transition. Many studies have pointed out that birth rates are inversely associated with both income and education, two indicators that have shown significant progress in the country, especially more recently (6).

1.1.3 Education

Education is regarded as a universal right and government funded. In 2010, approximately 5.8% of the Gross Domestic Product (GDP) was spent on education (3). Data from the National Households Sample Survey have shown that between 1992 and 2009 the average schooling levels among the Brazilian population raised from 5.8 years to 8.2 years of study (6). In 2008, approximately 95% of children and adolescents aged 7–17 years were enrolled in school (7). Although there has been an increase in school access, primary and secondary public education is still very deficient, and those who can afford it prefer private schools. According to the 2010 Brazilian Demographic Census, the literacy rate for the total population, defined as the percentage of those aged 15 and older who are able to read and write, was 90.4% (90.1% among males and 90.7% among females). However, among those aged 65 and over, about 29.4% are illiterate. The highest rates of illiteracy are found in the Northeast region (19.1% in 2010), and the lowest rates in the South (5.1%) (4).

1.1.4 Economy

Recently, Brazil has appeared in the international arena as one of the emerging economies that constitute a new group of countries (the BRICS, formed by Brazil, Russia, India, China and South Africa). According to the International Monetary Fund and the World Bank, Brazil is the largest economy in South America, and the seventh largest in the world in purchasing power parity (PPP) and in terms of market exchange rates. In 2014, Brazil's GDP per capita (PPP) was estimated as $12,528, ranking the country in the 77th position (8). In addition to presenting large and well-developed agricultural, mining, manufacturing, and service sectors, Brazil has been expanding its participation in the international markets and firmly improving its macroeconomic stability. In 2010, GDP growth rate reached 7.5% (the highest growth rate in the past 25 years), nevertheless rising inflation and the deteriorating international economic picture have slowed growth in 2011-2014. Currently, unemployment is at historic lows (unemployment rate is around 5.7%), although 21.4% of the population is still below the poverty line (which represents around 40 million people). Despite some

improvements, Brazil's fiscal and current account balances have eroded during the past three years, since the government has attempted to boost economic growth through targeted tax cuts for industry and incentives to spur household consumption. The level of poverty and income inequality remain high (Brazil is one of the world's leaders in terms of income inequality) and disproportionately affect the Northeast, North, and Center-West, women, and some ethnic groups (black, brown, and indigenous populations). Moreover, disparities in opportunities promote social exclusion and contribute to high rates of crime in the country (3).

1.1.5 Government and Politics

The government of Brazil is a federal republic, with a presidential system. Five fundamental principles constitute the basis of the Brazilian Federation: *"sovereignty, citizenship, dignity of human beings, the social values of labor and freedom of enterprise, and political pluralism"*. During most of its democratic history, Brazil has had a multi-party system, with proportional representation in the Congress. The president is both chief of state and head of government and is elected for a four-year period (re-election for a second term is also possible) (9). Dilma Rousseff is the current president (since 2011), and was the first woman to be elected president in Brazil.

1.1.6 Health Profile

During the past decades, mainly due to the progress in social determinants of health and establishment of a comprehensive national health system in 1989, Brazil has experienced important improvements in health status and life expectancy. Nevertheless, as a consequence of urbanization and social and environmental change, new health problems have emerged, while some old health issues still remain unabated (7).

Over the past forty years, life expectancy at birth has increased by more than 6 months per calendar year (in 1960, it was about 54.5 years; while in 2009 was 72.9 years). Underweight prevalence in children younger than 5 years has been reduced (from 5.6% in 1989, to 2.2% in 2006–07), and the under-5 mortality has been falling by 4.8% a year since 1990. Although maternal mortality trends have been difficult to measure with precision due to better reporting, modeled estimates have indicated an annual rate of decline of approximately 4%. Despite of those improvements, illegal abortions remain highly prevalent, along with increasing rates of preterm deliveries and over-medicalisation of child-birth (caesarean section rates are the highest in the world) (7).

It is noteworthy to mention that Brazil has shown striking or partial progress against the majority of infectious diseases (almost complete eradication of some vaccine-preventable diseases (polio, measles, and diphtheria), diarrhoea, and Chagas' disease; partial success in control of malaria, hepatitis A and B, tuberculosis and schistosomiasis; and low prevalence of HIV (<0.5%), which has been stable since 2000). However, the efforts to control dengue fever and visceral leishmaniasis have repeatedly failed. Increased deforestation and population mobility have expanded areas of transmission for some endemic diseases (e.g., yellow fever), and caused previously rural diseases to appear in urban areas (e.g., visceral leishmaniasis and leprosy). Additionally, environmental changes have been associated with emergence of new infectious diseases (e.g., Brazilian haemorrhagic fever and hantaviruses) (7).

Concomitant with falling smoking rates, mortality rates due to chronic diseases have decreased by 20% from 1996 and 2007, largely due to reductions in cardiovascular and chronic respiratory diseases. Nevertheless, hypertension, obesity, diabetes, and cancers have increased, and neuropsychiatric disorders are now the most important contributor to disease burden. Although homicides and traffic-related injuries / deaths have shown a slight decline, they still remain at epidemic levels (7).

Since 1989, all Brazilians have been entitled to free health care at primary, secondary, and tertiary level through a national health system, called the Unified Health System (SUS - Sistema Único de Saúde), funded by taxes and social contributions. With the establishment of the SUS, the access to primary health care through the Family Health Strategy has been increasing throughout the country. This change has caused recorded effects on infant, and possibly adult mortality, as well as reductions in unnecessary hospital admissions. A 2008 survey showed that 93% of those who sought health care were able to obtain it. Several intervention strategies for maternal and child health are now being delivered through the primary health care structure rather than as independent vertical programs, with almost universal coverage (7).

With respect to human resources for health, in 2007, only 1.7 doctors, 0.9 nurses, and 1.2 dentists were available per 1000 population. In order to increase the number of doctors, nurses, dentists, as well as public-health professionals and auxiliary health personnel, the Brazilian ministries of health and education have been investing heavily in new training programs. Even though currently health workers already represent about 10% of the Brazilian

workforce, many challenges remain, such as: uneven regional distribution of qualified personnel, high turnover, lack of structured careers, and major salary differences between regions, states, and municipalities (7).

1.2 BACKGROUND

1.2.1 Non-Communicable Diseases (NCDs)

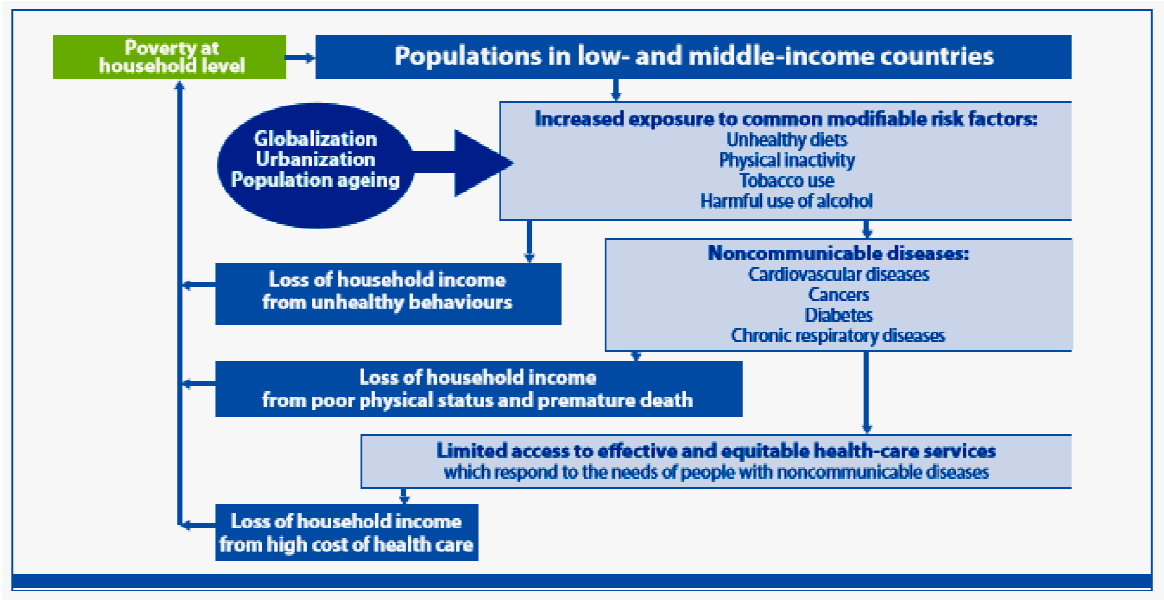
Non-communicable or chronic diseases can be described as diseases that present a long duration and usually a slow progression (10). This group of diseases, which include cardiovascular diseases (CVDs), cancers, chronic respiratory diseases, neuropsychiatric disorders and diabetes, has become a major global health problem and a relevant threat to human health and development (11).

NCDs are the leading cause of death worldwide, with a remarkably greater impact on the world's low- and middle-income populations. According to the World Health Organization (WHO), NCDs caused 63% of all deaths globally in 2008 (about 36 million deaths), and nearly 80% of those, particularly premature deaths, occurred in low- and middle-income countries (LMICs). Moreover, the total number of deaths from NCDs is projected to rise globally by 15% between 2010 and 2020, and the greatest increase is expected to be observed in LMICs (11). Concerning the global burden of disease, relevant increases in disability-adjusted life years (DALYs) have been expected to occur among many of the leading NCDs. For instance, DALYs attributable to cardiovascular diseases have been projected to rise from 11.1% in 1990 to 14.7% in 2020, whereas those due to neurological, mental, and substance use disorders, to rise from 10.5% to 14.7% in the same period (12).

In Brazil, a large middle-income country, NCDs have also become the main sources of morbidity and mortality. In 2007, 72% of all deaths were due to NCDs (CVDs, chronic respiratory diseases, diabetes, cancer, and others, including renal diseases), and only 10% to infectious or parasitic diseases. This figure contrasts with that found in 1930, when about 46% of all deaths were attributed to infectious diseases (13). According to a study published in 2004 concerning the disease burden in Brazil, NCDs have been responsible for 66% DALYs; while infectious, maternal, perinatal disorders and nutritional deficiencies have accounted for 24%; and external causes for 10% (14). Among the NCDs, neuropsychiatric disorders (including depression, psychoses and disorders attributed to alcohol misuse) are the single largest contributor to the disease burden in the country. In addition, the occurrence of hypertension and diabetes has been facing important increases as well as that of obesity (13).

To a large extent, NCDs are caused by four main behavioral risk factors (tobacco use, harmful use of alcohol, unhealthy diets and insufficient physical activity), which are pervasive features of rapid unplanned urbanization, economic transition, and 21st-century lifestyles. Reflecting the underlying socioeconomic determinants, the greatest impact of these risk factors falls increasingly on the most disadvantaged and vulnerable populations in the developing world. Poverty exposes people to the NCDs-related risk factors, and, in turn, the resulting NCDs and their significant costs of treatment and/or subsequent loss of employment and income push vulnerable individuals deeper into the poverty cycle. In many LMICs, the detection of NCDs has been done late, when most of the patients already require expensive hospital care for complications or acute events. Due to the high household spending on these diseases and their risk factors, less money becomes available for basic needs such as food and shelter (Figure 1.2) (11).

Figure 1.2: Poverty and NCDs Cycle



Furthermore, the considerable costs from NCDs to individuals, families, health systems and governments have also been associated with major macroeconomic effects. In some of the most populous countries of the globe, billions of dollars in terms of national income are lost each year, due to diabetes and cardiovascular diseases. It has been estimated by economic analysis that a 10% increase in NCDs is related to 0.5% lower rates of annual economic growth. Nevertheless, less than 1% of the 22 billions of dollars spent by international aid agencies on health problems are allocated for chronic diseases. Of note, the

growing epidemic of NCDs and its devastating socioeconomic consequences have caused a profound negative effect on the progress towards sustainable development goals. Therefore, in the absence of urgent and sustained action, the impact of NCDs will continue to rise and the goal of reducing poverty in the world will be significantly undermined (11).

On the positive side, strong evidence has shown that cost-effective, population-wide and individual interventions exist and can be successfully implemented in a wide range of resource settings. Through the reduction of the above mentioned risk factors, as well as through the control of other underlying metabolic / physiological factors (such as hypertension, obesity, dyslipidemia, and impaired glucose metabolism), NCDs can be largely prevented. Further strengthening of health systems to provide appropriate and cost-effective services, making possible an early detection and timely treatment of NCDs, is another important approach for reducing their impact. Nevertheless, adequate political commitment and full engagement of non-health sectors and key stakeholders are also essential in the promotion of stronger and more focused international and national responses to fight the NCDs epidemic (11).

1.2.2 Diabetes Mellitus (DM)

1.2.2.1 Definition, Classification and Diagnosis of DM

According to the WHO, DM can be defined as a heterogeneous metabolic disorder characterized by chronic hyperglycemia with abnormalities of carbohydrate, protein and fat metabolism. It results from defects in insulin secretion, insulin action, or both (15).

As reported by the American Diabetes Association (ADA), the classification of DM can be stated as follows (16):

- Type 1 Diabetes: accounts for 5-10% of the cases, and results from the destruction of the β-cells of the pancreas, which usually leads to absolute insulin deficiency.
- Type 2 Diabetes: responsible for ~90-95% of those with diabetes, and encompasses individuals with insulin resistance and usually relative, rather than absolute, insulin deficiency;
- Other specific types: genetic defects of β-cell function, genetic defects in insulin action, endocrinopathies, diseases of the exocrine pancreas, etc;

- Gestational Diabetes Mellitus (GDM): any degree of glucose intolerance that was initiated or first recognized during pregnancy.

Based on new knowledge generated from research and clinical practice, the recommendations for the diagnosis of DM have been changing over the years, concerning both the cutoff points and tests to be used. For decades, the diagnostic criteria of diabetes mellitus have mostly relied on glucose measurements, either by the Fasting Plasma Glucose (FPG) levels or the 2-h values in the 75-g Oral Glucose Tolerance Test (OGTT). Nevertheless, after extensive review of established and emerging evidence, the use of Glycated Haemoglobin (HbA1c) in the diagnosis of diabetes has been recommended by the WHO, ADA, and other international organizations (16).

According to the ADA, there are now four possible ways to diagnose diabetes (16):

1. *A1C ≥ 6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.**

   OR

2. *FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8h.**

   OR

3. *2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.**

   OR

4. *In a patient with classic symptoms of hyperglycemia (such as polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision) or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).*

**In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing, on a subsequent day.*

Additionally, as reported by the ADA (concerning individuals whose glucose levels do not meet criteria for DM, but present higher levels than those considered normal), the classification of the intermediate states of abnormal glucose regulation can be done as follows (17):

Table 1.1: Classification of Glucose Tolerance States according to the ADA

State	**FPG level, mg/dl (mmol/l)**	**2-h Plasma Glucose in OGTT, mg/dl (mmol/l)***
Impaired Fasting Glucose (IFG)	100–125 (5.6–6.9)	< 200 (< 11.1)
Isolated IFG	100–125 (5.6–6.9)	< 140 (< 7.8)
Impaired Glucose Tolerance (IGT)	< 126 (< 7.0)	140–199 (7.8–11.0)
Isolated IGT	< 100 (< 5.6)	140–199 (7.8–11.0)
Combined IFG/IGT	100–125 (5.6–6.9)	140–199 (7.8–11.0)
Normal Gucose Tolerance (NGT)	< 100 (< 5.6)	< 140 (< 7.8)

*Standard 75-g OGTT.

Of note, some studies have shown that, compared to the fasting glucose cutoff point of 100mg/dl (5.6mmo/l), an HbA1c cutoff point of 5.7% has a lower sensitivity but higher specificity as well as a higher positive predictive value to identify individuals at risk for future development of diabetes. Thus, an HbA1c range of 5.7 to 6.4% has been suggested to identify those with an increased risk for diabetes, and for CVDs (16).

On the other hand, according to the WHO, the values for the diagnosis of DM and other categories of hyperglycaemia are (18):

Table 1.2: Diagnosis of DM and other Categories of Hyperglycaemia (WHO Criteria)

	Glucose Concentration, mmol/l (mg/dl)*			
	Whole Blood		Plasma	
DM	Venous	Capillary	Venous	Capillary
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)	≥ 7.0 (≥ 126)
or				
2-h post glucose load**	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)	≥ 12.2 (≥ 220)
or both				
IGT				
Fasting (if measured)	< 6.1 (< 110)	< 6.1 (< 110)	< 7.0 (< 126)	< 7.0 (< 126)
and				
2-h post glucose load**	≥ 6.7 (≥ 120) and < 10.0 (< 180)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 8.9 (≥ 160) and < 12.2 (< 220)

IFG				
Fasting	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 6.1 (≥ 110) and < 7.0 (< 126)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
and (if measured)				
2-h post glucose load**	< 6.7 (< 120)	< 7.8 (< 140)	< 7.8 (< 140)	< 8.9 (< 160)

** "For epidemiological or population screening purposes, the fasting or 2-h value after 75 g oral glucose may be used alone. For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms".*
*** "If 2–h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded" (19).*

In a report published in 2011, the WHO also states that HbA1c can be used as a diagnostic test for diabetes. A value of 6.5% was recommended as the cut point for diagnosing DM. However, an HbA1c less than 6.5% does not exclude DM diagnosed using glucose tests (20).

1.2.2.2 Prevalence and Trends of DM Worldwide and in Brazil

Costly and burdensome, diabetes is now a huge-scale pandemic and one of the most challenging public health problems in the 21st century. Poorly managed diabetes is associated with dysfunction and failure of several organs (specially the eyes, nerves, kidneys, heart, and blood vessels), which can cause disability, decreased quality of life, and reduced longevity. Dramatic increases in the incidence and prevalence rates of diabetes, particularly type 2 diabetes mellitus (T2DM), have taken place in the past decades worldwide, along with growing numbers of premature deaths. Previously considered "a disease of the wealthy", developing countries are now facing a firestorm of diabetes and its disabling and life-threatening complications, following demographic ageing, and profound environmental, lifestyle and occupational changes. Currently, approximately 80% of the 382 million people with diabetes in the world live in LMICs. It has been estimated that this number of people with diabetes will increase by 55% by the year 2035, and the greatest growth will be observed in the developing nations. Additionally, impaired glucose tolerance (IGT) - early metabolic abnormality preceding diabetes, that greatly increases the risk of developing T2DM and is also linked with the occurrence of CVDs - has also become a major public health problem, with projections for further rises (Figure 1.3) (21).

Figure 1.3: Global Prevalence and Projections of Diabetes and IGT

AT A GLANCE	2013	2035
Total world population (billions)	7.2	8.7
Adult population (20-79 years, billions)	4.6	5.9
DIABETES AND IGT (20-79 YEARS)		
Diabetes		
Global prevalence (%)	8.3	10.1
Comparative prevalence (%)	8.3	8.8
Number of people with diabetes (millions)	382	592
IGT		
Global prevalence (%)	6.9	8.0
Comparative prevalence (%)	6.9	7.3
Number of people with IGT (millions)	316	471

According to the International Diabetes Federation (IDF), in South and Central America, about 8% of the adult population (24.1 million people) have diabetes, while 7.4% (22.4 million) have IGT. By the year 2035, it has been expected that the number of people with diabetes in the region will rise by nearly 60%, to almost 38.5 million (21).

In Brazil, a large population-based survey (known as the Brazilian Multicenter Study) conducted on a representative sample (n = 21,847) of the urban population aged 30 to 69 years in nine large cities between 1986 and 1988, showed that the prevalence of DM was 7.6 and that of impaired glucose tolerance 7.8%, without significant differences between genders. However, the DM prevalence in the 60-69-yr age-group was 17.4% (22). More recently, between 1996 and 1997, another cross-sectional study conducted in Southeastern Brazil found that the overall rates of diabetes and impaired glucose tolerance were 12.1 and 7.7%, respectively, while the rates for the 60-69 year age group were 21.7% and 11.3%, respectively (23).

Currently, according to the IDF, Brazil has an overall estimated diabetes prevalence of 9%, and it is the country in the South and Central America region with the highest number of people with the disease (11.9 million), followed by Colombia (2.1 million) and Argentina (1.6 million). It has also been projected that by the year 2035 there will be 19.2 million Brazilians with diabetes, which will rank Brazil in 4th place among the countries with the highest numbers of people with diabetes in the world (21).

1.2.2.3 Associated Factors for DM

Although the specific etiologies of type 2 diabetes still remain uncertain, the condition is thought to be developed from an interaction between lifestyle and genetic factors. It has been shown that the activation of genes that predispose an individual to diabetes requires the presence of behavioral and environmental factors. It is interesting to note that the most significant increases in T2DM have taken place precisely among populations in which rapid and major lifestyle changes have occurred. According to the IDF, the risk factors for T2DM can be classified as non-modifiable and modifiable as stated below (24):

- Non-modifiable Risk Factors:

- Genetic Factors: The genetics of type 2 diabetes is complex and not clearly defined (16). Studies have found that some ethnic groups present a significant higher prevalence of T2DM compared to others, when exposed to similar environments (for instance, indigenous populations in North America, Pacific Islanders, Australian Aborigines, people of Asian and African origin, etc) (24). Additionally, it has been shown that individuals with a family history of T2DM are at a higher risk of developing the disease, even though identifying genetic variants that can explain such excess risk has been a challenge (25).
- Age: Although the prevalence of T2DM increases remarkably with older age, its occurrence has risen in children and adolescents in recent years (21).
- History of GDM: Despite glucose tolerance usually returning to normal after the delivery, women who have had GDM are at a greater risk of developing T2DM later in life as well as developing GDM in subsequent pregnancies. Their babies also present a higher lifetime risk of obesity and developing T2DM (21).
- Polycystic Ovary Syndrome (PCOS): Women with PCOS have been found to be insulin resistant, have defects in insulin secretion, and be at a higher risk of IGT and T2DM (26).

- Modifiable Risk Factors:

- Overweight and Obesity: Several studies have shown that obesity is the most important risk factor for T2DM. Interventions targeted to decrease obesity have also reduced T2DM incidence. The prevalence of overweight and obesity are increasing dramatically worldwide, not only among adults but also among children and adolescents. According to the 2008 WHO estimates, more than half a billion adults were obese worldwide, with the highest prevalence rates found in the Americas. In

Brazil, about 51.7% and 18.8% of the population were overweight and obese respectively (11, 24, 27).

- Physical Inactivity: Both cross-sectional and longitudinal studies have shown that physical inactivity is an independent predictor of T2DM. Considering the same levels of obesity, more physically active individuals have a lower incidence of T2DM (24). Although the rates of insufficient physical activity are highest in high-income nations, considerable levels have also been seen in some middle-income countries (11). In a nationwide survey conducted in 1996 in Brazil, only 3.3% of the adults reported doing 30 minutes of leisure-time physical activity, at least 5 days a week (13).
- Nutritional Factors: It has been suggested that a high total calorie and low dietary fiber intake, a high glycemic load and a low polyunsaturated to saturated fat ratio may contribute to the development of T2DM (24). Although repeated national surveys of dietary patterns have not been conducted in Brazil, data from 4 representative surveys of family food expenditure conducted from the mid-1970s to the mid-2000s have indicated a decrease in the purchase of traditional food items (rice, beans and vegetables), and a great rise (around 400%) in the purchase of processed foods (processed meat, cookies, soft drinks, etc) (13).
- Previously identified glucose intolerance (IGT and/or IFG): As previously mentioned, people with IGT and/or IFG are at high risk of developing T2DM. Nevertheless, healthy diet and physical exercise have been documented to be effective in preventing the progression to diabetes (21).
- Metabolic Syndrome (MS): Over the past decades, a dramatic increase in the number of people with MS has occurred globally. Although several definitions have been issued to identify individuals with MS, those most widely used share some core characteristics: glucose intolerance, central obesity, insulin resistance, dyslipidemia (decreased high-density lipoprotein cholesterol - HDL-c -, increased triglycerides - TG -), and hypertension (all well documented risk factors for CVDs). It has been indicated that the risk for T2DM in the MS is high, ranging between three- and 20-fold (28).
- Intrauterine environment: It has been indicated that intrauterine exposure to diabetes per se conveys a high risk for diabetes and obesity in the offspring that is above any genetically transmitted susceptibility (29). It has also been hypothesized that poor fetal and early post-natal nutrition may be detrimental to the development and function of the endocrine pancreas, predisposing the individual to the occurrence of

T2DM later in life (30). Although some authors have suggested that an inverse linear relation exists between birth weight (BW) and risk for T2DM, a recent meta-analysis has indicated that such relation is U-shaped and not linearly inverse, meaning that not only low BW (as previously thought), but also high BW are associated with later-life increased risk of diabetes (31).

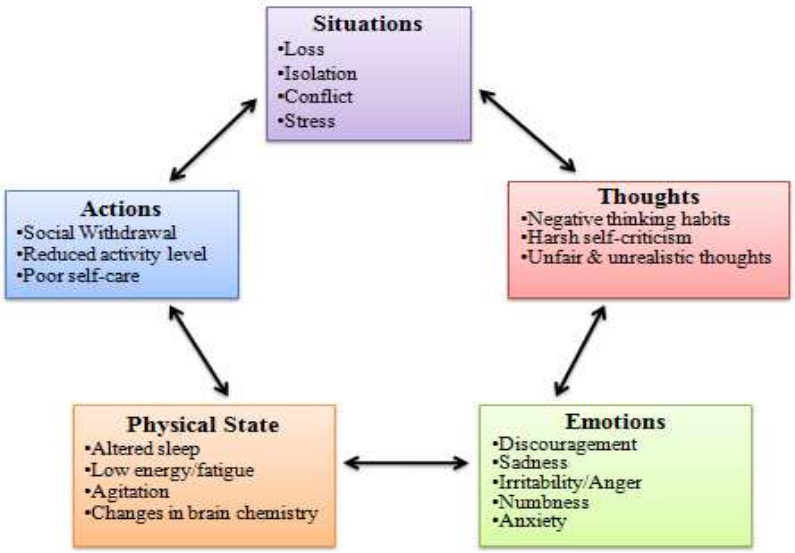
- Inflammation: In the past years, it has been found that chronic low-grade inflammation (increased levels of cytokines such as C-reactive protein - CRP - , tumor necrosis factor α -TNF-α, etc) plays an important role in the development of T2DM (32).

1.2.3 Depression

1.2.3.1 Definition, Etiology / Pathophysiology, Classification of Mood Disorders and Diagnosis of Depression

The general term "depression" can be used in a number of different ways. It may refer to a state of mood, a symptom manifesting itself in many different mental disorders, a syndrome or a clinical diagnosis (33). Commonly, depression or more specifically major depression or unipolar depression can be described as a heterogeneous mood disorder characterized by depressed mood, loss of interest or pleasure, thoughts of death and suicide, fatigue and loss of energy, poor concentration, feelings of guilt or low self-worth, and disturbed sleep or appetite. Moreover, depression is often accompanied by symptoms of anxiety, and may present a highly variable course, as well as an inconsistent response to treatment (34, 35). It has been postulated that approximately one third of the risk for the development of depression is inherited and two thirds is environmental (36). Furthermore, studies have shown that depression occurs as a result of complex interactions between social, psychological and biological factors. Life situations, thoughts, emotions, physical state and actions have been identified as major factors that contribute to the development and maintenance of depressive symptoms (Figure 1.4), while depression can, in turn, lead to more stress and dysfunction and worsen the life situation of the affected individual (37, 38).

Figure 1.4: Depression and the Complex Interactions with Social, Psychological and Biological Factors



For many years, psychiatrists and neuroscientists have attempted to better elucidate the biology of depression. Despite its complexity and heterogeneity, substantial progress has been made in our understanding of its underlying pathophysiology (39). There are many theories that seek to identify a biochemical origin of depression. Among them, the *Monoamine Hypothesis* (Monoamines are neurotransmitters and neuromodulators, including serotonin, dopamine, norepinephrine, and epinephrine), despite its multiple limitations, has been considered one of the most prominent and widely researched. According to this hypothesis, a deficiency of certain neurotransmitters in the brain (i.e., dopamine, norepinephrine, and seretonin) is responsible for the corresponding features of depression (40). Additionally, hormone levels and the stress response have also been investigated in depressed individuals. One of the most enduring and reproducible findings in biological psychiatry is the hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis in some patients with depression. The HPA axis consists of a complex set of direct influences and feedback interactions involving the hypothalamus, pituitary and adrenal glands. In addition, the axis also receives regulation from other structures in the brain (e.g., the hippocampus, amygdala, paraventricular nuclei, etc). As a major part of the neuroendocrine system, the HPA axis plays an essential role in maintaining the body homeostasis, by adapting the organism to changes in the internal and external environments. It controls reactions to stress and regulates many body processes, including digestion, the immune system, mood and

emotions, sexuality and energy storage and expenditure. During a physical or emotional stressor, the axis is activated. The hypothalamus secretes two hormones (corticotropin-releasing hormone - CRH, and arginine vasopressin - AVP), which will cause an increase in the release of the adrenocorticotropin hormone (ACTH) from the pituitary. Then, ACTH is carried in the blood to the adrenal cortex and stimulates the production and secretion of cortisol. Finally, the loop is completed by the negative feedback of cortisol to the hypothalamus and pituitary (41). Cortisol is a stress hormone, that stimulates the production of glucose, increases lipolysis and circulating free fatty acids, as well as decreases insulin secretion from beta cells and insulin sensitivity (42). In depression, it has been shown that a continual activation of the HPA axis and an impaired negative feedback control take place, as well as adrenal hypertrophy. CRH is hyper secreted from the hypothalamus, which increases the release of ACTH, and consequently the cortisol levels are raised. The cortisol receptors become desensitized, which results in increased activity of the pro-inflammatory immune mediators, and disturbances in noradrenalin and serotonin transmission (43). Of note, it has been known for many years that approximately 50% of all depressed individuals have a sustained elevation of plasma cortisol levels. Thus, it has been postulated that chronically high levels of cortisol result in obesity, insulin resistance and type 2 diabetes (42).

Even though depression is related to the normal emotions of sadness and bereavement, when the external cause of these emotions dissipates, depression does not remit and it is usually out of proportion to their cause. It is important to note that it takes more than just tearfulness or short-lived emotional responses to challenges in everyday life to indicate the presence of depression (35). In order to establish a diagnosis of clinical depression or major depressive disorder (MDD), a detailed and careful history of symptoms, thoughts, feelings and behavior patterns must be collected from the individual and from others (other family members, for example), in addition to a systematic evaluation for mental status, as well as specialized tests and investigations as needed. Relevant progress has been made during the past decades concerning the standardization of clinical assessment and the reliability of the diagnosis. Uniform definitions of signs and symptoms, structured and semistructured standardized interview schedules, and standard diagnostic criteria have provided the grounds for achieving a high degree of reliability in the diagnosis of mental disorders (44, 45). According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association in 2013, the mood disorders mainly include (46):

- Major Depressive Disorder;

- Persistent Depressive Disorder (previously called dysthymic disorder): state of chronic low mood most of the time for at least two years, often with fewer or less serious symptoms than major depression;
- Bipolar Disorder (also known as manic-depression or manic-depressive disorder): characterized by mood that alternates between two emotional extremes, or poles: the sadness of depression and the euphoria of mania;
- Cyclothymic Disorder: milder yet more enduring type of bipolar disorder, in which a person's mood alternates between a less severe mania (hypomania) and a less severe depression;
- Mood Disorder due to a General Medical Condition: significant disturbance in mood (including either / or both: 1) Depressed mood or significantly reduced level of interest or pleasure in most or all activities. 2) Mood that is euphoric, heightened, or irritable), that is directly related to the presence of a medical condition;
- Substance / Medication-Induced Depressive Disorder: significant disturbance in mood, with symptoms of either depressed or euphoric mood (or both) that develop during (or within four weeks of) intoxication or withdrawal, or are caused by medication use;
- Disruptive Mood Dysregulation Disorder: condition in which a child up to age 18 years exhibits persistent irritability and frequent episodes of extreme behavioral dyscontrol;
- Premenstrual Dysphoric Disorder: condition in which a woman has severe depression symptoms, irritability, and tension before menstruation.

Furthermore, according to the DSM-5, for the diagnosis of MDD, single episode (46):

- At least five of the nine symptoms below must have been present for the same two weeks or more, and this represents a change from previous functioning. One of the symptoms must be either (a) depressed mood, or (b) loss of interest.
    1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. For children and adolescents, this may be characterized as an irritable mood.
    2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Difficulty falling or staying asleep (insomnia), or sleeping more than usual (hypersomnia) nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others).
6. Fatigue or loss of energy nearly every day.
7. Thoughts of worthlessness or excessive or inappropriate guilt nearly every day.
8. Diminished ability to think, or concentrate, or indecisiveness, nearly every day.
9. Recurrent thoughts of death or suicide (with or without a specific plan), or suicide attempt.

- The symptoms do not indicate a mixed episode.
- The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
- The symptoms are not due to the direct physiological effects of a substance (e.g., alcohol, drugs, medication), or a general medical condition (e.g., hypothyroidism).

1.2.3.2 Prevalence and Trends of Depression Worldwide and in Brazil

Currently, it is estimated that depression affects about 350 million people all over the world (34). Due to its relatively high lifetime prevalence worldwide, and its association with substantial disability and premature mortality, depression has become an important global public health priority. Additionally, depression has been associated with large decrements in quality of life and daily functioning (47), as well as increased absenteeism and reduced productivity at work (48). The co-occurrence of depression with other chronic diseases such as angina, arthritis, asthma, and diabetes, incrementally worsens health compared with depression alone, with any of the chronic disorders alone, and with any combination of chronic diseases without depression. Ranked as the fourth leading cause of burden among all diseases in 2000, depression accounted for 4.4% of total DALYs (49). It has been projected that by the year 2020, depression will be the second biggest contributor to the burden of disease worldwide, while it will be the first leading cause of DALYs in developing regions (12).

In the past decades, several large-scale epidemiological studies have been conducted in order to estimate the rates of depression. Although there have been many efforts to compare the prevalence and incidence rates of depression across different countries, these comparisons have been usually problematic since different study designs, sampling methods, diagnostic tools, and statistical analyses have been used worldwide. Nevertheless, the availability of large-scale community surveys using similar methods has made the comparison possible. A cross-national collaborative group including investigators from 10 countries (the United States, Canada, Puerto Rico, France, West Germany, Italy, Lebanon, Taiwan, Korea, and New Zealand) has reported that the lifetime rates for major depression varied widely across the countries, ranging from 1.5 cases per 100 adults in Taiwan to 19.0 cases per 100 adults in Beirut. The annual rates ranged from 0.8 cases per 100 adults in Taiwan to 5.8 cases per 100 adults in New Zealand (50). Concerning the global trends of depression, although many longitudinal studies have shown an increasing prevalence, this finding is not universal. Surveys conducted in the United States, Sweden, Germany, Canada, and New Zealand, using comparable methods and modern diagnostic criteria, have found a clear increase in the risk of depression over time. Nevertheless, in studies from Puerto Rico and South Korea, for instance, no increase in lifetime prevalence was found (51).

In Latin America, rare population-based studies of depression have been conducted, and most of them have used diagnostic methods of low reliability, thus producing descriptive data with limited application for mental health planning. In Brazil, the currently available estimates are mainly based on very few population-based surveys of psychiatric morbidity (52). A cross-sectional study (n=6,476) carried out in 1997 in order to estimate the prevalence of DSM-III psychiatric diagnoses in three large cities of Brazil (Brasília, São Paulo and Porto Alegre), has found prevalence rates of depression as 1.9%, 2.8% and 10.2%, respectively (53). Another survey from 2002 conducted in two boroughs of São Paulo, according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria, showed that 45.9% of the total sample (n=1,464) had at least one lifetime diagnosis of mental disorder, 26.8% in the year, and 22.2% in the month prior to interview. Mood disorders had the second highest prevalence, and among them, depressive episode had the greatest occurrence (prevalence of lifetime diagnosis: 16.8%, 12-month: 7.1%, and 1-month: 4.5%) (54). Additionally, a survey from 2001 carried out in a small Brazilian community, also according to ICD-10 criteria, found that lifetime, 1-year and 1-month prevalence rates of depression were 15.6%, 10.0% and 8.2% respectively. Of note, the

1-month prevalence found in this community was unexpectedly higher than that observed in similar studies from other developed and developing countries. Since psychiatrists and other mental health professionals in Brazil are usually concentrated in big cities, and the health services in small communities are often not adequately prepared to approach mental health disorders, it is likely that depression is a major unidentified condition in such communities (52).

1.2.3.3 Associated Factors for Depression

The occurrence of depression has been associated with a number of medical, psychosocial and demographic factors (33).

It has been consistently found that women suffer from higher rates of depression than men (33, 55). Although the reasons still remain unclear, many attempts have been made in order to explain such phenomenon. The explanations include the possibility that this sex difference in rates does not reflect the reality because of artifacts produced by methods of reporting symptoms (women perceive, acknowledge, report, and seek help for stress and symptoms differently than men and these factors account for the sex ratio findings), or that they are legitimate because of biological susceptibility (genetic transmission and female endocrine physiological processes), and psychosocial factors (the long-standing disadvantaged social status of women, or female-learned helplessness) (56). Furthermore, it has been observed that this sex difference is age specific. Whereas a notable sex difference has been found in middle life, the difference has not been relevant in either childhood or advanced old age (33).

The relationship between depression and age has been given considerable research attention, however the studies have reached conflicting results, with greatly varying patterns of age group differences (57). In Brazil, according to the previously mentioned study conducted in São Paulo in 2002, the highest rates for mood disorders were found among people between 25–54 years old (54). However, a large population-based study conducted in Norway (n=62,344) showed that both the mean level as well as the number of cases of depression increased close to linearly with age (56). Yet some American studies have shown that depressive symptoms were most prevalent in younger women and tended to decrease with age, whereas the prevalence in men increased with age. Other studies from Europe have observed an increase in depressive symptoms in women up to late middle age, and a decrease thereafter, while no age trend was found among men (33).

Some other factors that have been reported as important predictors of depression include low income, illiteracy, lack of social support, as well as alcohol and smoking habit (58, 59). Additionally, marital status has also been connected with the onset and prevalence of depression. It has been observed that depression occurs more often among widowed and divorced persons compared to those who are married, never got married or are cohabiting (59).

Higher rates of depression have been found frequently in patients with several medical conditions, such as myocardial infarction, DM, human immunodeficiency virus (HIV)-related illness, cancer, cerebrovascular accident, Parkinson's disease, etc. The progressive functional impairment associated with many chronic medical illnesses may result in depression, and depression is associated with additive decrements in function. Increasing evidence indicates that both depressive symptoms and MDD may be associated with increased morbidity and mortality from conditions such as DM and heart disease. The adverse effect of depression on health habits (smoking, unhealthy diet, and sedentary lifestyle), its negative impact on adherence to medical regimens, as well as direct adverse physiologic effects (i.e., decreased heart rate variability, increased adhesiveness of platelets) may explain this association with higher morbidity and mortality rates (60).

Numerous studies have also shown that a positive family history of depression is associated with an increased risk of the condition in offspring. Although it is likely that part of that effect is genetic, it has also been reported that even after controlling for the familial effect, little parental socio-economic status (low level of education and occupational status) increases the risk of offspring depression (61). Additionally, trauma in early life, including childhood physical or sexual abuse, has been strongly connected with the occurrence of depression in adult life (62).

1.2.4 Relationship between Diabetes and Depression

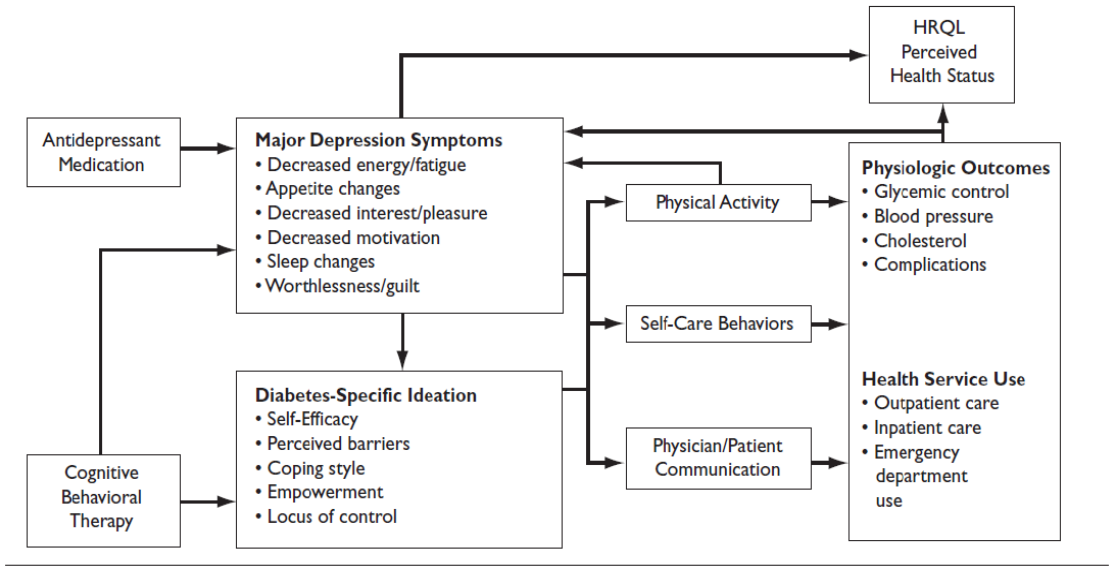
As previously mentioned, diabetes and depression are common and rapidly increasing NCDs throughout the world. Both are related to significant reductions in life expectancy, decreased quality of life, as well as increased functional disability (63).

The association between the two conditions was first noted in the literature in 1684 when Thomas Willis suggested that diabetes was the result of sadness or prolonged sorrow (64). After that time, research on this relationship was sparse until the past 20 years. Lately,

many studies have found a frequent co-existence of depression, hyperglycemia, diabetes and diabetes-related complications. Moreover, comorbid depression in diabetes has been associated with poorer adherence to diabetes treatment regimens (65), decreased work productivity and increased disability (66), lower quality of life (67), higher rates of retinopathy and macrovascular complications (68), as well as increased mortality rates, beyond that due to having either diabetes or depression alone (69). A recent meta-analysis of longitudinal studies indicated that depressed adults have a 37% increased risk of developing type 2 diabetes. The findings of such meta-analysis have also suggested that depression could be considered as an additional risk factor for T2DM, even comparable in size to physical inactivity and smoking (42). Conversely, another meta-analysis showed that diabetes doubles the odds of co-morbid depression (70). Furthermore, some studies have indicated that depression may cause a negative impact on glycemic control (which may result in increased occurrence of complications and disability), and improvements in depressive symptoms may lead to a significantly better diabetic control (71, 72). On the other hand, better glycemic control in patients with type 2 diabetes may result in better mood and general well-being, and fewer physical symptoms (73, 74). It has been estimated that depression is neither recognized nor treated in approximately two thirds of subjects with both the conditions, and also presents a chronic and severe course in these patients (74). Additionally, this co-morbidity has been associated with higher health care costs, and the implementation of more effective depression screening programs and depression treatment for patients with diabetes might lead to a decreased economic burden and better clinical outcomes (75).

In order to promote a better understanding of the impact of depression on diabetes care and treatment outcomes, an interesting conceptual framework has been developed by Piette at al. (Figure 1.5) (68).

Figure 1.5: Conceptual Framework Linking Depression to Diabetes Outcomes



HRQL indicates health-related quality of life.

According to this model, there are four main pathways through which depression may affect the outcomes among patients with both diabetes and depression:

1. Depression produces a direct impact on health-related quality of life, as well as on physical, social, and role functioning of patients with both depression and diabetes. Thus, even if diabetes-related pathophysiology and outcomes do not change, by addressing the patients' depressive symptoms, an improvement on their quality of life will probably take place.
2. Diabetes patients with co-morbid depression are more likely to present low levels of physical activity. Studies have suggested that patients who are more physically active present better diabetes-related outcomes, while those who are less physically active are more likely to develop depression. The promotion of physical activity may be a treatment approach that can improve both patients' physiologic risk factors for complications associated with diabetes and their mental health.
3. It has been suggested that depression affects patients' self-care behaviors. Depressed patients are less likely to optimally manage their diabetes self-care due to their lack of energy and motivation, negative pattern of cognition, as well as their passive coping strategies.
4. Depressed patients are more likely to establish an impaired patient-provider communication, and consequently they are less likely to follow through on the recommended treatment plans, which may lead to poorer outcomes. Furthermore,

probably because of poor adherence, decreased self-care and difficult interactions with providers, depressed patients tend to use more health services and have higher healthcare costs.

The figure also indicates a theoretical effect of treating depression with medication and focused counseling. Successful depression treatment may result in a greater self-efficacy for diabetes care, which is associated with better glycemic control and global funtioning (68).

Although there is a growing body of evidence showing the association between diabetes and depression, the direction of this relationship and the exact pathophysiological mechanisms behind it are still not fully understood. While one line of investigation lends support to the hypothesis that depression is a consequence of diabetes, another line of research seeks to demonstrate that depressive symptoms are a risk factor for the development of diabetes. Furthermore, it has also been suggested that the answer for such a conundrum may not be as a simple as a unidirectional relationship, and rather that the co-morbidity of diabetes and depression is part of a bidirectional interaction between the two conditions (76).

1.2.4.1 Depression as a Consequence of Diabetes

The increased risk of depression among individuals with diabetes has been frequently conceptualized as having two possible mechanisms. First, the psychosocial burden of having a chronic medical condition like diabetes may promote the development of depressive symptoms. It has been observed that when the burden of diabetes increases, the probability of mood symptoms also increases. Perceived disability and awareness of having a chronic disease such as diabetes may impose higher levels of psychological stress, especially among those with poor social support. Additionally, diabetes requires high levels of self-care (proper medication management, strict dietary regimens, frequent monitoring of blood glucose values), may generate medical complications and decreased mobility, which can contribute to a negative psychological impact. Second, biochemical factors associated with diabetes, may also result in an increased risk of depression. For instance, hyperglycemia and hyperinsulinemia increase the activity of the HPA axis, inducing arousal of the nervous system, which in turn may lead to depression (76, 77).

A large-scale research study conducted in the Netherlands, after adjustment for lifestyle and demographic variables, found that individuals with diagnosed T2DM had nearly 2 times increased risk of depressive symptoms compared to those without a diagnosis. However, no significant increased risk of depressive symptoms was seen in subjects with

impaired FPG concentration and undiagnosed T2DM. Similarly to some other studies, these findings suggest that the psychosocial burden of a chronic disease, rather than the disturbed glucose homeostasis, is associated with depression (77). Nevertheless, there have also been studies providing evidence that depression is a consequence of the diabetes pathophysiological process itself, above and beyond the burden of a chronic disease. For instance, in the Vietnam Experience Study, data from over 4,000 male veterans were collected to investigate the link between fasting glucose values, diabetes diagnosis, and depression. It was observed that both known and undiagnosed diabetes were associated with an increased risk of depressive symptoms. Men with undiagnosed T2DM were almost twice as likely to have major depression compared to those with normal fasting glucose concentrations (78).

1.2.4.2 Depression as a risk factor for the onset of diabetes

The idea that depression is a risk factor for the development of diabetes has been often explained by two possible ways. Some studies have indicated that depressive symptoms such as reduced interest or pleasure in activities, sleep and appetite dysregulation, fatigue, and decreased ability to think or concentrate can make individuals with depression less likely to engage in health-promoting behaviors. Thus, depression has been associated with higher BMI, consumption of hypercaloric diets, sedentary lifestyle and smoking, which can ultimately lead to T2DM (76). Additionally, it has also been suggested that a low intake or impaired metabolism of omega-3 polyunsaturated fatty acids (PUFAs) may contribute to both diabetes and depression; even though the evidence on fatty acid levels in diabetic depressive patients is still sparse (42).

On the other hand, it has also been suggested that the biochemical changes associated with depression or its treatment may promote a cascading effect that results in the onset of diabetes. As described previously, depression is associated with increased activity of the HPA axis (higher release of cortisol) and sympathetic nervous system (SNS), and increased production of proinflammatory cytokines (associated with endocrine changes and greater risk of diabetes). Chronically elevated cortisol levels increase the risk of developing metabolic syndrome (characterized by central adiposity, or excess accumulation of abdominal fat, and insulin resistance), which also increases the risk of developing diabetes. Concerning depression treatment, there has been research showing an association of some types of selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants with

hyperglycemia and increased risk of diabetes (76). However, a recent intervention study conducted among 26 non-diabetic Pakistani women with newly diagnosed depression showed a significant improvement of insulin sensitivity following the treatment of depression with citalopram (a type of SSRI that has not shown significant effects on insulin sensitivity or changes in glycaemic control) (79).

1.2.4.3 Evidence for a bidirectional relationship

It has been hypothesized that a reciprocal interaction underlies the relationship between depression and diabetes. Depression and related genetic, biological, and psychosocial factors may increase the risk for T2DM onset and subsequent diabetes complications. On the other hand, consequences of these complications may include increased illness intrusiveness and emotional distress, thereby increasing the risk for depression (76).

A meta-analysis published in 2008 showed that subjects with T2DM have a 15% increased risk of depression compared to those without diabetes, and depressed people have a 60% increased risk of developing T2DM (80). Additionally, Golden et al. also identified a bidirectional longitudinal association between depressive symptoms and T2DM. In this study, individuals with normal glucose levels and elevated depressive symptoms were at an increased risk for developing T2DM over three years, whereas those with T2DM and little depressive symptomatology at baseline were at an increased risk of developing depressive symptoms over the same period (81).

1.3 RATIONALE AND SIGNIFICANCE OF THE STUDY

As mentioned previously, the association between depression and diabetes has been observed by several (82); however, the transcultural validity of these findings still needs to be demonstrated (83). Since social and cultural factors have been found to influence the prevalence of psychiatric disorders, it is likely that the occurrence of depression in people with diabetes will present variations among and within societies (84). Therefore, the relationship between diabetes and depression should preferably be studied in different cultural environments (83). In Brazil, few studies have been published about this topic and, to the best of our knowledge, no research based on representative community surveys, including different age groups, has come out so far. Thus, it remains unclear whether these findings on

the association between the two conditions reported in some countries are similar in a middle-income country like Brazil.

In addition, Brazil has experienced a rapid demographic and economic transition, with profound consequences to the society as a whole and more specifically to nutritional and lifestyle patterns. Industrialization, urbanization and an increasing globalization of unhealthy food habits among other factors have exposed the Brazilian population to greater risks of chronic diseases, including diabetes and depression (13).

Many studies conducted elsewhere may have been biased, since they have been largely conducted in specialized diabetic centers or elderly homes with a large number of older patients (many of which already have other complications). Moreover, these data have been collected from prevalent cases of diabetes or depression and many have used self-reported data on diabetes. Older age is known to be related with other different chronic diseases, and the presence of multiple chronic conditions in addition to diabetes may impact negatively on the quality of life and increase functional limitations, which may contribute to the onset of depression. Thus, the occurrence of depression in people with pre-existing diabetes may have been overestimated (83). This research project recruited participants from the general population, and depression and diabetes were evaluated simultaneously. The diagnosis of diabetes was not disclosed to them before the assessment of depression was completed. Therefore, it is likely that the debated confounding factor of the duration of a chronic disease, like diabetes, leading patients to depression could be avoided.

All the data collected are likely to contribute for the development of strategies to prevent diabetes, depression and possibly cardiovascular diseases as well. New approaches for the treatment of diabetes may be developed by including the treatment of depression for possible improved glycaemic control. Timely treatment and strategies to prevent complications applied to the participants who were diagnosed with diabetes, depression and / or another medical condition may reduce morbidity, mortality and lifelong complications. Furthermore, the results of this study may add some important knowledge to the general understanding of the relationship between diabetes and depression, which in turn may lead to a better management of both the conditions; and they may also give grounds to the development of new hypotheses for exploration and new management and preventive guidelines.

1.4 HYPOTHESIS

Higher prevalence of depression among people with newly diagnosed diabetes compared to those without diabetes in a city in the northeast of Brazil.

1.5 RESEARCH QUESTIONS

- What is the prevalence of diabetes? What is the prevalence of depression?
- Is there an association between diabetes and depression in this population?

1.6 OBJECTIVES

- Main Objective:
  - To investigate the prevalence of type 2 diabetes and depression, and the association between depressive symptoms and newly diagnosed diabetes in Brazil.

- Specific Objectives:
  - To assess the prevalence of diabetes and depression among people aged 20 years and above.
  - To investigate the prevalence of depression among people with newly diagnosed diabetes compared to those without diabetes in northeastern Brazil.
  - To identify the risk indicators of diabetes and depression including biophysical (blood pressure, anthropometry, body fat percentage) and biochemical (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol) parameters.
  - To examine the association of different measures of obesity (BMI, WHR and body fat percentage) and its association with diabetes and / or depression.
  - To assess the association of plasma cortisol levels with the occurrence of depression and diabetes.
  - To assess the agreement between two measures of depression (MADRS: Montgomery-Åsberg Depression Rating Scale; and HDRS: Hamilton Depression Rating Scale) in the studied population.

CHAPTER 2

MATERIALS AND METHODS

2.1 STUDY AREA

The study was conducted in the city of Pindoretama, located in the state of Ceará (CE), in the northeast region of Brazil (Figure 2.1). With a land area of approximately 75 square kilometers, the city is approximately 40 km far from the main town of the state (Fortaleza). According to the IBGE, in 2010 Pindoretama had around 18,683 inhabitants, a population density of 256 people per square kilometer, and a sex ratio of 0.99 male/female (4).

Figure 2.1: Geographical Location of Pindoretama in Brazil

In 2012, the GDP per capita was estimated as $1,700 (85), while in 2010 approximately 13.97% of the total population were considered extremely poor (household income per capita less than $25.00/month). In 2010, the illiteracy rate among those aged 15 and older was 21.70% (86).

In 2012, Pindoretama had six main primary healthcare centers and one secondary care hospital affiliated to the Unified Health System. In 2011, there were around 1.0 physicians/1,000 inhabitants, 0.7 nurses/1000 inhabitants, 0.58 dentists/1,000 inhabitants and 40 community health workers (CHWs) (86).

Pindoretama was chosen as the location to carry out the study based on some practical criteria, such as: availability of nearby laboratory facilities and adequate places to make the examinations and investigations; support from the local health and governmental authorities;

availability of nurse assistants and health volunteers willing to be trained and participate in the execution of the study, etc.

2.2 STUDY DESIGN AND POPULATION

This population-based research study was based on a cross-sectional design, and was conducted over a period of approximately 6 months (from August, 2012 to January, 2013). The study collected data from 714 subjects who were residents in Pindoretama – CE.

2.3 SAMPLE SELECTION

2.3.1 Inclusion Criteria

- Subjects of both genders;
- Age ≥ 20 years;
- Being able to communicate;
- Willing to join the study.

2.3.2 Exclusion Criteria

- Subjects below 20 years of age;
- Pregnant women;
- Physically or mentally disabled individuals who were unable to follow simple questions and examinations.

Following the above mentioned exclusion criteria, eight hundred and six randomly selected subjects were invited to participate. Out of these, seven hundred and fourteen agreed to join the study.

Additionally, when analyzing the association between diabetes and depression, those presenting at least one of the following characteristics were excluded:

- Individuals reporting a current diagnosis of type 2 diabetes and / or depression;
- History of Gestational Diabetes Mellitus (GDM);
- Previous diagnosis of type 1 diabetes;
- Acute or chronic severe cardiac, renal or hepatic illnesses;
- Current use of anti-depressants for any reason.

In total, eighty two subjects were excluded from the analysis of the association between diabetes and depression.

2.3.3 Sample Size Calculation

The required sample size to this study was determined using the following formula:

$$N = 2 \cdot [z_{crit} \sqrt{2\bar{p}(1-\bar{p})} + z_{pwr} \sqrt{p_1(1-p_1) + p_2(1-p_2)}]^2 / D^2,$$

where N is the total sample size, p_1 and p_2 are pre-study estimates of the two proportions to be compared ($p1 = 0.318 \rightarrow$ prevalence of depression among people with diabetes, and $p_2 = 0.195 \rightarrow$ prevalence of depression among those without diabetes. These prevalence rates were taken from a previous study (87)), $D = |p_1 - p_2|$ (the minimum expected difference) i.e. 0.123, $\bar{p} = (p_1 + p_2)/2$, i.e. 0.256, z_{crit}= 1.96 (Standard Normal Deviate for a Significance Criterion = 0.05 and a Confidence Interval = 0.95), and z_{pwr}= 1.282 (Standard Normal Deviate for a Statiscal Power = 0.90). Two-tailed statistical analyses were used.

$$\text{Thus, } N = 2 .[1.96 . 0.617 + 1.282 . 0.609]^2 / 0.015 = 527.46$$

After the addition of an estimated 10% drop-out rate, a number of approximately 580 was reached.

2.3.4 Sample Selection Process

The estimated sample size was randomly (using simple randomization methods) drawn from a population above 20 years of age, of both genders, using the health registry list of the city.

2.4 DATA COLLECTION

2.4.1 Survey Procedures

Prior to the survey, the selected subjects were contacted by the CHWs in order to be invited to join the study. By the time of invitation, the CHWs briefly informed the potential respondents about the purposes of the study and methods of investigation. The necessary information and arrangements to assemble the participants in the study locations were organized. The data collection took place in the six main community health centers that are strategically located throughout the city (the initial time was different in different centers, but

within 6 months). In general, one month was spent on the fieldwork in each center. Thus, within that month, the subjects could choose the most appropriate day of the week to attend the survey.

The participants were instructed twice (personally by the CHWs and by a phone call at the previous day of the data collection) to start fasting from 8 pm of the night before the blood glucose level measurements. The survey procedures were carried out between 6 and 8 am. First, after the participants' arrival to the study place, the details about the research purpose and the investigations to be performed were explained again. Those who wanted to participate were given the informed consent. Then, venous blood samples were collected for FPG measurements. So, the subjects took a 75g oral glucose load (according to the WHO guidelines) in order to be prepared to the OGTT. They were also interviewed, with the use of questionnaires regarding socio-demographic, economic and physical activity information. The MADRS and HDRS were used to assess depression, and by this time, neither the participants nor the investigators were aware of the subjects' plasma glucose level results. Anthropometric, blood pressure and body fat percentage measurements were also taken. Another blood sample was collected two hours after the 75g oral glucose load. Capillary HbA1c measures were taken after the assessment of depression. Finally, a morning meal was given to the participants.

2.4.2 Research Team Training and Fieldwork Supervision

One experienced nurse assistant highly qualified in venipuncture was responsible to draw the blood samples from the participants. Another nurse assistant was trained by the principal investigator, under the supervision of the local supervisor (Professor Renan Magalhães Montenegro Júnior), to conduct the capillary HbA1c assessment. Socio-demographic, economic and physical activity data were collected by one research assistant that was adequately trained before the start of the study. Anthropometric, blood pressure and body fat percentage measurements were taken by another research assistant who was also carefully trained by the principal investigator, under the supervision of the local supervisor (Professor Renan Magalhães Montenegro Júnior). A nurse with experience in mental health disorders conducted the MADRS, while the HDRS was performed by the principal investigator. Both of them had prior experience of assessing depressive scores. They received proper training during five days and conducted the interviews under the supervision of an experienced psychiatrist (Professor Fábio Gomes de Matos e Souza, local supervisor).

All procedures performed in the study and methods of efficient data collection were

discussed among the team members. During the fieldwork, the principal investigator encouraged the research team members to discuss all problems faced and their potential solutions.

2.4.3 Pretesting of Questionnaires

Pretesting of the questionnaires to assess general information, socio-demographic, economic, medical and physical activity data was conducted among 10 subjects in the local community in order to assess their feasibility, and catch and solve unforeseen problems. As a result, the wording of the questionnaires was improved, unnecessary questions were eliminated and others were added. Adjustments were made in order to reduce the length of time required to complete the survey.

2.4.4 Interviewer-Guided Questionnaires

2.4.4.1 Questionnaire to Assess General Information, Socio-Demographic, Economic and Medical Data

The questionnaire to assess general information, socio-demographic, economic and medical data was developed based on the existing literature and related experience. Face-to-face interviews were conducted in the study sites.

The most relevant variables are described below:

- *General information, socio-demographic and economic features:*
    - Age;
    - Gender;
    - Ethnicity → following the IBGE classification, the participants were asked about their self-perception of the skin color, and the different ethnic groups were categorized into: "white", "brown", "black", "yellow" (i.e. east Asian) and "indigenous";
    - Marital Status → categorized into "married", "single", "divorced or separated", "cohabitant", "widow/er";
    - Level of Education → number of years of institutional education was recorded. Years of education were further categorized into "illiterate", "primary school", "high school", and "university or higher";
    - Occupation → categorized into "student", "agriculture", "industry and services", "domestic labour" (housewives or those who worked in other houses

performing domestic tasks, such as cleaning, cooking, etc), "construction" (mainly masons), "sick benefit" (those who were away from work due to some temporarily disabling condition), "retired", "unemployed", "other" (other occupations that did not fit in the previous categories). The various types of occupations were further subdivided into two groups: "manual labor" (types of occupations that usually entail moderate to high level of physical activity, such as jobs in agriculture and construction), and "not manual labor" (those who were retired, unemployed, students, etc, or types of occupations that entail low levels of physical activity, such as jobs in industries, services, etc).

- Monthly Income → individual income per month. It was categorized into "low" (income lower or equal to 1 minimum wage in 2012, that corresponds currently to US$ 218.00), "middle" (income between 1 and 5 minimum wages), and "high" (income higher or equal to 5 minimum wages).

- *Individual history of diseases:* the participants were asked about past and current diagnosis of some relevant diseases (hypertension, diabetes type 1 and 2, depression, cardiovascular diseases, cancer, etc). Use of medication was also investigated.
- *Family history of diseases:* it was defined as having a father, mother, brother or sister with a diagnosis of type 2 diabetes, depression, cardiovascular disease, etc.
- *Lifestyle:*
    - Smoking Habits → categorized into "never", "previous mild", "previous heavy", "current mild" and "current heavy". Previous was defined as those who have stopped smoking for at least 6 months. Current: those who currently smoke or have stopped smoking for less than 6 months. Mild: less than 20 cigarettes/day. Heavy: more than 20 cigarettes/day.
    - Alcohol Consumption → categorized into "no", "once a month or less", "2 to 4 times a month", "2 to 3 times a week", "4 or more times a week".
    - Diet → the frequency of consumption of various types of food and beverages was assessed. It was measured by using four categories, ranging from "never" to "daily". The different items were further categorized into "fat" (fat used for cooking and on the bread, full cream milk and yoghurt), "carbohydrates" (bread, noodles, biscuits, cookies, roots, rice, wheat, tubers, etc), "sugars" (fruits, chocolates, cola with sugar), "protein" (beef, chicken, pork, fish, eggs, etc) and "vegetables".

2.4.4.2 International Physical Activity Questionnaire (IPAQ)

The interview administered IPAQ short form was applied to assess physical activity data. IPAQ short form is an instrument designed primarily for population surveillance of physical activity among adults (age range of 15-69 years). It assesses the time spent on walking, in vigorous- and moderate intensity activity and in sedentary activity. IPAQ assesses physical activity undertaken across a comprehensive set of domains including: 1) Leisure time physical activity; 2) Domestic and gardening (yard) activities; 3) Work-related physical activity; and 4) Transport-related physical activity (88). The items in the IPAQ short form were structured to provide separate scores on walking, moderate-intensity and vigorous-intensity activity. Computation of the total score for the short form requires summation of the duration (in minutes) and frequency (days) of walking, moderate-intensity and vigorous-intensity activities. Domain specific estimates cannot be estimated. According to the guidelines for data processing and analysis, the levels of physical activity are categorized into "low", "moderate" and "high" (89). In a study conducted in 12 countries including Brazil, data concerning the reliability and validity of the IPAQ short and long forms were collected. The results showed that the IPAQ instruments exhibited acceptable measurement properties, that were at least as good as other established self-report physical activity measures (90).

2.4.4.3 Assessment of Depression

The MADRS and the HDRS were used for the assessment of depression scores. The MADRS is a 10-item questionnaire (the score of each item ranges from 0 to 6, and the total sum for the 10 items can range from 0 to 60), that takes about 10-15 minutes to be performed. Its scores are usually categorized into four groups: 0-12 (healthy), 13-19 (mild depression), 20-34 (moderate depression) and 35-60 (severe depression) (91). In this study, total scores between 0 and 19 were considered as absence of depression, whilst scores $\geq$ 20 were taken as presence of depression. The HDRS is a 17-item questionnaire (eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe, while nine are scored from 0-2), that generally takes 15-20 minutes to be administered. Usually, scores above or equal to 23 identify very severe depression; between 19 and 22, severe depression; 14-18, moderate depression; 8-13, mild depression; and 0-7, normal (92). In this study, total scores of 0-13 were considered as absence of depression, whilst scores $\geq$ 14 indicated depression. Of note, the term "depression" applied here refers to an epidemiological definition of depression based on a threshold level of symptom scales, rather than a clinical diagnosis.

2.4.5 Anthropometric Measurements

Four anthropometric measures were taken, without shoes and with light clothes: weight, height, hip and waist circumferences.

The weight was taken by using a portable digital scale, placed on a flat surface, with the subject placing the arms by side, face forward and waiting still, and recorded to the nearest 0.1 Kg. The height was measured by using a well-mounted stadiometer, recorded to the nearest 0.1 cm, with the participant looking straight (keeping the tragus and the lateral orbital margin in the same horizontal plane), and in erect position. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters (Kg/m^2). The WHO classification of BMI was applied (Underweight: BMI < 18.5; Normal: BMI between 18.5 and 24.99; Overweight: BMI between 25 and 29.99; Obesity: BMI ≥ 30) (93).

The waist circumference was taken by placing a non-stretchable measuring tape horizontally on the midpoint between the lower part of the 12^{th} rib and the top of the iliac crest, under the mid-axillary line. It was measured at the end of normal expiration, with the arms relaxed by the sides. To the hip girth measurement, a similar tape was positioned to the maximum circumference around the buttocks, with the subject standing straight, keeping hands by the sides, and facing palms inward. Waist and hip circumference were recorded to the nearest 0.1 cm. The waist-to-hip ratio (WHR) was calculated as the waist measurement divided by the hip measurement. Following the WHO cut-off points, for males, a WHR ≥ 0.90cm was considered "high", i.e., substantially increased risk of metabolic complications, whereas for females a WHR ≥ 0.85cm was classified as "high" (94).

2.4.6 Measurement of Body Fat Percentage (BF%) - Bioelectrical Impedance Method

The BF% was measured by a portable bipolar body fat analyzer (Omron®, Model HBF-306). The device works by a formula that calculates the fat percentage by taking into account gender, age, weight, height, and the electric resistance encountered by the micro currents (500 μA, 50 kHz) that are emitted from one hand grip, pass through the limb, torso and the next limb to the other hand grip, where the fluctuation in the value is recorded. The BF% measurement is displayed almost instantly (within 7 seconds). The BF% was measured with the participant holding the hand grips on both sides, standing up straight, with arms slightly outstretched and making a 90 degree angle with the chest. The "normal mode" was used.

2.4.7 Measurement of Blood Pressure (BP)

BP was measured twice, by using an electronic sphygmomanometer (Omron® BP785 IntelliSense® Automatic Blood Pressure Monitor with ComFit^{TM} Cuff). The subjects were asked to relax and the first measurement was taken after a resting time of at least 15 minutes, while the second approximately 5 minutes after the first. The participants were sitting with legs uncrossed and the left arm was used to the measurements. The mean value of two measurements was used for analysis.

2.4.8 Biochemical Assessments

Peripheral venous blood samples were collected after at least 8 hours fasting from all study participants. The collected samples were transferred to a sterile container and stored immediately over ice and then centrifuged within approximately 1 hour of collection. Plasma was frozen and transported (within 2 hours) on dry ice, in vaccine carriers to the laboratory where the samples were stored at – 20° Celsius until the analyses were performed. The first fasting sample (10 ml) was used to carry out the analyses for the estimations of plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), cortisol and insulin levels. The second sample (3ml) was analyzed for the estimation of plasma glucose levels after a 75g oral glucose load (OGTT). Fasting and 2-h plasma glucose levels were analyzed by glucose oxidase method, whereas fasting insulin was determined by chemiluminescence. Capillary HbA1c levels were measured by A1CNow® Multi-Test A1C System (Bayer). Total cholesterol was estimated by CHOD-PAP (cholesterol oxidase - phenol + aminophenazone) method, while HDL-C was determined by a homogenous enzymatic colorimetric method. Triglycerides were determined by GPO-PAP (glycerol-3-phosphate oxidase - phenol + aminophenazone) method. Low-density lipoprotein cholesterol (LDL-C) was estimated by using the Friedewald Formula (95). Cortisol was analyzed by chemiluminescence (Beckman Coulter). Quality control of the laboratory was assessed internally and externally.

2.5 CATEGORIZATION OF DM, IFG, ISOLATED IFG, IGT AND ISOLATED IGT

The diagnosis of diabetes was based on both fasting and 2h-plasma samples for comparative analysis, according to the WHO criteria (18), i.e. fasting (venous) plasma

glucose value ≥ 7.0mmol/l (≥ 126mg/dl), or the plasma glucose value 2 hours after a 75g oral glucose load ≥ 11.1mmol/l (≥ 200mg/dl), or both.

IFG cases were defined as those with FPG values ≥ 6.1 and < 7.0mmol/l (≥ 110 and < 126mg/dl), while isolated IFG cases were those with FPG values ≥ 6.1 and < 7.0mmol/l (≥ 110 and < 126mg/dl) and 2-h plasma glucose in OGTT < 7.8mmol/l (< 140mg/dl).

IGT cases were those with 2-h plasma glucose in OGTT ≥ 7.8 and < 11.1mmol/l (≥ 140 and < 200mg/dl), whereas isolated IGT cases were defined as those with FPG values < 6.1mmol/l (< 110mg/dl) and 2-h plasma glucose in OGTT ≥ 7.8 and < 11.1mmol/l (≥ 140 and < 200mg/dl).

2.6 STATISTICAL METHODS

2.6.1 Data Management

All information collected by questionnaires, clinical examinations and biochemical analyses were registered in a computer database by using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Missing values and data entry errors were checked carefully.

2.6.2 Data Handling

Numerical data were presented as means and 95% confidence intervals (CIs), while categorical data as percentages and 95% CIs. The prevalence rates of diabetes and depression were determined by simple percentages. Chi-square tests were used to evaluate differences among categorical variables; t-tests and one-way analysis of variance (ANOVA) evaluated differences in continuous variables. Initial univariate analysis was carried out to determine whether selected independent variables were significantly associated with the occurrence of diabetes or depression. Multiple logistic regression models were used to control for potential confounding factors. The crude and multivariate-adjusted ORs, as well as 95% CIs were presented. They were calculated assuming the least prevalence of clinically relevant criteria as the reference value. A p-value < 0.05 was considered statistically significant and all p-values presented were two-tailed.

Agreement between MADRS and HDRS, as well as between FPG and 2-h values in the 75-g Oral Glucose Tolerance Test (OGTT) were evaluated by the kappa statistic (poor - kappa < 0; slight - kappa: 0.01–0.20; fair - kappa: 0.21– 0.40; moderate - kappa: 0.41–0.60;

substantial - kappa: 0.61–0.80; and almost perfect - kappa: 0.81–0.99) (96). Bivariate Pearson's correlation coefficient was also used to evaluate the correlation between the depression scores assessed by MADRS and HDRS.

All statistical analyses were performed by using the software SPSS 22 version. The graphs were constructed by using the software Stata 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

2.7 ETHICAL CONSIDERATIONS

The study was conducted following the Helsinki Declaration of medical research. It was approved by the local Ethical Committee in Brazil, as well as by the Regional Committee for Research Ethics in Norway.

Prior to the survey, a local meeting with local health authorities, CHWs and research team members was organized by the principal investigator. The purposes of the study and survey procedures were discussed and everyone was requested to give comments about the study. Their suggestions were incorporated into the study design.

Written or verbal consent from all subjects was obtained prior to any investigation. In case of illiteracy, verbal consent was assured by a local witness (who could sign the informed consent) in order to secure the subjects` free participation. Prior to enrollment in the study, CHWs read out a paragraph to each potential respondent that described the purpose of the study and methods of investigation. At the day of data collection, the details about the research purpose, the investigations and examinations to be conducted, as well as the risks and benefits involved were explained again by the principal investigator. All respondents were informed of their right to refuse to take part in the research, withdraw from the study at any stage or to withhold their data from analysis. They were also reassured that there would not be any consequences of refusing to participate. Those who were not interested in joining the study were not included.

The confidentiality of all health data gathered was ensured by limiting the accessibility of the information to the main investigators. Furthermore, each participant was assigned a unique identification number and all data were referenced to this number rather than a name. The information was kept in a locked cabinet and data analysis did not include identifying information.

Only qualified and trained health personnel were responsible to collect the blood samples, and precautions were made to prevent injuries. The risk of contracting blood borne diseases to both health personnel and participants was minimized by using good hygienic and protective measures while investigating, and collecting blood samples. In the examination of participants` anthropometric measurements, their privacy was maintained. To alleviate the problems, the participants were given a choice to be examined in a separate room, or in a place with screens. The removal of hats, clothes, etc in order to carry out the anthropometric measurements was done only if the participant agreed so.

Questioning on sensitive issues when carrying out the depression scales (pessimistic and suicidal thoughts for example) was handled carefully in order to minimize any psychological burden. The participants were treated with respect and every effort was made to ensure their physical and emotional comfort. A medical doctor was present at the survey settings to manage any clinical problems that might happen.

The written results of medical examinations were distributed and explained to the participants. All subjects who were diagnosed with any clinical condition were referred to the respective health center for further follow up.

CHAPTER 3

RESULTS

Data were collected from 714 subjects including new and previous cases of T2DM and depression. However, when analyzing the association between diabetes and depression (prevalence and logistic regression models), the data are restricted to the subjects noted as newly diagnosed diabetes (NDD) (n = 632). The results will be presented into 5 parts:

3.1 Descriptive analysis of the study population.

3.2 Diabetes:

3.2.1 Prevalence of DM, IFG, isolated IFG, IGT and isolated IGT;

3.2.2 Characteristics of the study population with and without diabetes;

3.2.3 Socio-demographic / behavioural and clinical factors associated with diabetes / univariate and multivariate analyses.

3.3 Depression:

3.3.1 Prevalence of depression according to MADRS and HDRS;

3.3.2 Characteristics of the study population with and without depression;

3.3.3 Socio-demographic / behavioural and clinical factors associated with depression / univariate and multivariate analyses.

3.4 Relationship between diabetes and depression (MADRS and HDRS):

3.4.1 Characteristics of the study sample with or without diabetes / depression;

3.4.2 Prevalence of DM among depressed subjects and prevalence of depression among diabetics compared to disease-free individuals;

3.4.3 Univariate and multivariate regression models.

3.5 Correlation between HDRS and MADRS.

3.1 DESCRIPTIVE ANALYSIS OF THE STUDY POPULATION

The baseline characteristics of 714 subjects are shown in tables 3.1 and 3.2. The mean ages of men and women were 46.17 and 44.57 respectively. BMI, hip circumference, body fat percentage, 2-hour Plasma Glucose, LDL-C, fasting insulin, as well as MADRS and HDRS scores were significantly higher in females compared to males, whereas WHR and SBP were significantly lower in females compared to male subjects (Table 3.1).

Table 3.1: Baseline Characteristics of 714 Subjects by Gender from Northeastern Brazil

Variables	**Males (n=242)**	**Females (n=472)**	**Total (n=714)**
Continuous Variables	*Mean (95% CI)*	*Mean (95% CI)*	*Mean (95% CI)*
Age (years)	46.17 (44.15-48.20)	44.57 (43.12-46.02)	45.11 (43.93-46.29)
BMI (Kg/m^2)	25.89 (25.35-26.44)	27.36 (26.86-27.86)**	26.87 (26.48-27.25)
Waist circumference (cm)	89.49 (87.91-91.08)	90.32 (89.13-91.51)	90.04 (89.09-90.99)
Hip circumference (cm)	95.53 (94.41-96.65)	100.14 (99.18-101.11)**	98.58 (97.82-99.34)
WHR	0.94 (0.92-0.95)	0.90 (0.89-0.91)**	0.916 (0.907-0.924)
Body Fat Percentage	24.96 (24.01-25.92)	36.81 (36.19-37.43)**	32.78 (32.12-33.45)
SBP (mmHg)	133.39 (130.54-136.26)	124.71 (122.60-126.80)**	127.65 (125.93-129.36)
DBP (mmHg)	77.83 (76.17-79.49)	76.25 (74.53-77.97)	76.78 (75.52-78.05)
FPG (mmol/l)	5.26 (4.98-5.54)	5.59 (5.35-5.83)	5.48 (5.29-5.67)
2-hour Plasma Glucose (mmol/l)	7.39 (6.87-7.91)	8.09 (7.66-8.53)*	7.86 (7.52-8.20)
Capillary HbA1c (%)	6.22 (6.07-6.36)	6.37 (6.25-6.48)	6.31 (6.22-6.41)
Total Cholesterol (mmol/l)	4.62 (4.49-4.74)	4.76 (4.67-4.85)	4.71 (4.64-4.78)
Triglycerides (mmol/l)	1.73 (1.44-2.03)	1.45 (1.33-1.58)	1.55 (1.42-1.68)
HDL-C (mmol/l)	1.23 (1.22-1.24)	1.22 (1.21-1.23)	1.22 (1.21-1.23)
LDL-C (mmol/l)	2.74 (2.62-2.86)	2.91 (2.83-3.00)*	2.86 (2.79-2.92)
Fasting Cortisol (mcg/dl)	14.03 (13.55-14.50)	14.20 (13.69-14.72)	14.14 (13.77-14.52)
Fasting Insulin (micro UI/ml)	5.57 (5.01-6.13)	7.38 (6.91-7.85)**	6.77 (6.40-7.14)
MADRS score	5.79 (4.88-6.69)	9.60 (8.79-10.41)**	8.31 (7.68-8.94)
HDRS Score	4.70 (4.02-5.38)	7.53 (6.95-8.11)**	6.57 (6.11-7.03)

CI: Confidence Interval. BMI: Body Mass Index. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. FPG: Fasting Plasma Glucose. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. MADRS: Montgomery-Åsberg Depression Rating Scale. HDRS: Hamilton Depression Rating Scale.
BMI, waist circumference, hip circumference, WHR, FPG, 2-hour Plasma Glucose, HDL-C and MADRS scores have 1 missing value; SBP and DBP have 2 missing values; capillary HbA1c has 3; fasting cortisol and triglycerides have 5; total cholesterol has 6; fasting insulin has 11; body fat percentage has 16; and LDL-C has 35 missing values.
The value in men had a significant difference compared to that in women at *p<0.05 or **p<0.01 by Independent Samples T test.

There was also a significant difference between males and females with regard to the types of ethnicity, education and monthly income levels, marital status, smoking and alcohol habits, amounts of physical activity, and fat intake (Table 3.2).

Table 3.2: Baseline Characteristics (Cont.) of 714 Subjects by Gender from Northeastern Brazil

Variables	Males (n=242)	Females (n=472)	Total (n=714)
Categorical Variables	*% (95% CI)*	*% (95% CI)*	*% (95% CI)*
Ethnicity*			
White	11.6% (8.1-16.3)	19.5% (16.2-23.3)	16.8% (14.2-19.7)
Brown	84.7% (79.6-88.7)	78.6% (74.7-82.1)	80.7% (77.6-83.4)
Black	3.7% (1.9-7.0)	1.9% (1.0-3.6)	2.5% (1.6-3.9)
Education**			
Illiterate	19.4% (14.9-24.9)	10.2% (7.7-13.2)	13.4% (11.0-16.0)
Primary School	57.9% (51.5-63.9)	57.8% (53.3-62.2)	57.8% (54.2-1.4)
High School	20.6% (16.0-26.2)	27.1% (23.3-31.3)	24.9% (21.9-28.2)
University or Higher	2.1% (0.9-4.9)	4.9% (3.3-7.2)	3.9% (2.7-5.6)
Monthly Income**			
Low (≤ 1MW)	35.8% (29.9-42.1)	76.1% (71.9-79.7)	62.5% (58.9-65.9)
Middle (1MW - 5MW)	62.9% (56.6-68.8)	23.5% (19.9-27.6)	36.8% (33.3-40.4)
High (≥ 5MW)	1.3% (0.4-3.8)	0.4% (0.1-1.7)	0.7% (0.3-1.7)
Occupation			
Student	1.2% (0.4-3.8)	1.3% (0.6-2.8)	1.3% (0.7-2.4)
Agriculture	15.7% (11.6-20.9)	0.4% (0.1-1.7)	5.6% (4.1-7.6)
Industry and Services	40.1% (34.1-46.4)	23.9% (20.3-28.0)	29.4% (26.2-32.9)
Domestic Labour	0.8% (0.2-3.3)	43.0% (38.6-47.5)	28.7% (25.5-32.1)
Construction	11.2% (7.8-15.8)	0%	3.8% (2.6-5.5)
Sick Benefit	0%	0.8% (0.3-2.2)	0.6% (0.2-1.5)
Retired	24.8% (19.7-30.6)	20.3% (16.9-24.2)	21.7% (18.9-25.0)
Unemployed	2.9% (1.4-5.9)	4.8% (3.1-6.9)	4.1% (2.8-5.8)
Other	3.3% (1.7-6.5)	5.5% (3.8-7.9)	4.8% (3.4-6.6)
Marital Status**			
Single	18.6% (14.2-24.0)	24.3% (20.5-28.3)	22.3% (19.4-25.5)
Married / Cohabitant	74.8% (68.9-79.9)	62.8% (58.4-67.1)	66.9% (63.4-70.3)
Divorced / Separated	4.5% (2.5-8.0)	3.6% (2.3-5.7)	3.9% (2.7-5.6)
Widow(er)	2.1% (0.9-4.9)	9.3% (7.0-12.3)	6.9% (5.2-8.9)
Family History DM (yes)	43.0% (36.9-49.3)	38.3% (34.1-42.8)	39.9% (36.4-43.6)
Family History Depression (yes)	12.8% (9.1-17.7)	12.9% (10.2-16.3)	12.9% (10.6-15.6)
Smoking**			
Never	50.0% (43.7-56.3)	65.0% (60.0-69.2)	59.9% (56.3-63.5)
Previous Mild	18.2% (13.8-23.6)	14.3% (11.3-17.7)	15.5% (13.1-18.4)
Previous Heavy	11.2% (7.8-15.8)	1.9% (1.0-3.6)	5.2% (3.7-6.9)
Current Mild	16.1% (12.0-21.3)	16.7% (13.6-20.4)	16.5% (14.0-19.4)
Current Heavy	4.5% (2.5-8.0)	2.1% (1.1-3.9)	2.9% (1.9-4.5)
Alcohol Consumption in the last 12 months**			
No	47.1% (40.9-53.4)	72.3% (68.0-76.1)	63.7% (60.1-67.2)
Once a month or less	22.3% (17.5-28.0)	18.6% (15.4-22.4)	19.9% (17.1-23.0)
2 to 4 times a month	26.0% (20.9-32.0)	8.1% (5.9-10.9)	14.1% (11.8-16.9)

2 to 3 times a week	2.9% (1.4-6.0)	0.4% (0.1-1.7)	1.3% (0.7-2.4)
4 or more times a week	1.7% (0.6-4.3)	0.6% (0.2-2.0)	1.0% (0.5-2.0)
Physical Activity**			
Low	55.3% (49.0-61.5)	72.1% (67.8-75.9)	66.4% (62.8-69.8)
Moderate	33.5% (27.8-39.7)	21.8% (18.3-25.8)	25.8% (22.7-29.1)
High	11.2% (7.8-15.8)	6.1% (4.3-8.7)	7.8% (6.1-10.1)
Food Intake			
Sugar			
Low (never - 3 times a month)	0%	0.6% (0.2-2.0)	0.4% (0.1-1.3)
Medium (1 - 6 times a week)	12.0% (8.4-16.7)	11.1% (8.5-14.2)	11.4% (9.2-13.9)
High (Daily)	88.0% (83.3-91.6)	88.3% (85.1-91.0)	88.2% (85.7-90.4)
Carbohydrate			
Low (never - 3 times a month)	0.9% (0.2-3.3)	0.7% (0.2-2.0)	0.7% (0.3-1.7)
Medium (1 - 6 times a week)	1.2% (0.4-3.8)	0.6% (0.2-2.0)	0.8% (0.4-1.9)
High (Daily)	97.9% (95.1-99.1)	98.7% (97.2-99.4)	98.5% (97.2-99.1)
Protein			
Low (never - 3 times a month)	0%	0%	0%
Medium (1 - 6 times a week)	97.1% (94.0-98.6)	96.4% (94.3-97.8)	96.6% (95.0-97.7)
High (Daily)	2.9% (1.4-6.0)	3.6% (2.2-5.7)	3.4% (2.3-5.0)
Fat**			
Low (never - 3 times a month)	7.9% (5.1-12.0)	2.2% (1.1-3.9)	4.1% (2.8-5.8)
Medium (1 - 6 times a week)	26.4% (21.3-32.4)	20.3% (16.9-24.2)	22.4% (19.5-25.6)
High (Daily)	65.7% (59.5-71.4)	77.5% (73.5-81.1)	73.5% (70.2-76.6)
Vegetables			
Low (never - 3 times a month)	7.0% (4.4-11.0)	11.0% (8.5-14.2)	9.7% (7.7-12.1)
Medium (1 - 6 times a week)	9.1% (6.1-13.4)	5.5% (3.8-8.0)	6.7% (5.1-8.8)
High (Daily)	83.9% (78.7-88.0)	83.5% (79.8-86.6)	83.6% (80.7-86.2)

CI: Confidence Interval. MW: Minimum Wage in 2012, that corresponds currently to US$ 218.00. DM: Diabetes Mellitus.
Marital status has 1 missing value, and monthly income has 2 missing values.
Physical Activity level was measured by using the International Physical Activity Questionnaire (IPAQ).
Smoking → Previous: defined as those who have stopped smoking for at least 6 months; Mild: less than 20 cigarettes/day. Heavy: more than 20 cigarettes/day.
The value in men had a significant difference compared to that in women at *p<0.05 or **p<0.01 by Chi-square test or Fisher's Exact test.

Clinical characteristics of the study subjects by ethnicity are described in table 3.3. A borderline non-significant difference regarding the mean values of capillary HbA1c was found between whites and browns (p = 0.054). However, there was no significant difference among the three types of ethnicity concerning all the other clinical characteristics.

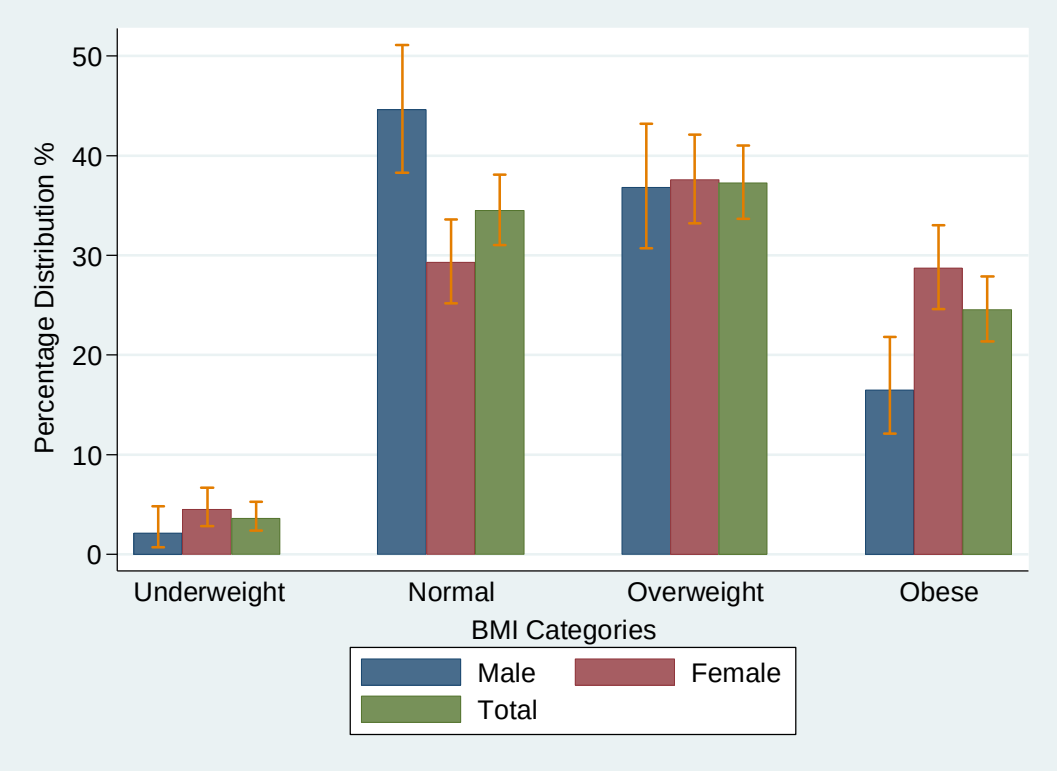
Table 3.3: Clinical Characteristics of 714 Subjects from Northeastern Brazil by Ethnicity

	White	Brown	Black
n = 714	120	576	18
	Mean (95% CI)	*Mean (95% CI)*	*Mean (95% CI)*
FPG (mmol/l)	5.26 (4.83-5.70)	5.54 (5.33-5.75)	4.98 (4.18-5.78)
2-hour Plasma Glucose (mmol/l)	7.43 (6.81-8.04)	7.96 (7.57-8.36)	7.43 (5.27-9.60)
Capillary HbA1c (%)	6.08 (5.92-6.23)*	6.37 (6.26-6.47)*	6.26 (5.81-6.71)
Fasting Cortisol (mcg/dl)	14.60 (13.61-15.58)	14.08 (13.67-14.50)	13.06 (10.94-15-19)
Fasting Insulin (micro UI/ml)	6.75 (5.98-7.52)	6.81 (6.39-7.24)	5.51 (3.56-7.46)
Total Cholesterol (mmol/l)	4.59 (4.41-4.78)	4.73 (4.65-4.81)	4.89 (4.38-5.40)
Triglycerides (mmol/l)	1.30 (1.16-1.44)	1.60 (1.44-1.75)	1.63 (1.04-2.21)
HDL-C (mmol/l)	1.23 (1.20-1.25)	1.22 (1.21.1.23)	1.23 (1.18-1.28)
LDL-C (mmol/l)	2.79 (2.61-2.96)	2.87 (2.79-2.94)	2.98 (2.47-3.49)
BMI (Kg/m^2)	26.92 (25.97-27.86)	26.91 (26.49-27.33)	25.08 (22.23-27.93)
Body Fat Percentage	33.73 (32.14-35.32)	32.70 (31.96-33.43)	29.43 (23.55-35.31)
WHR	0.90 (0.88-0.91)	0.92 (0.91-0.93)	0.95 (0.85-1.05)
SBP (mmHg)	128.04 (123.60-132.48)	127.57 (125.67-129.46)	127.56 (116.20-138.92)
DBP (mmHg)	75.53 (73.23-77.83)	77.10 (75.61-78.59)	75.14 (69.63-80.65)
MADRS score	7.77 (6.32-9.22)	8.40 (7.69-9.11)	8.83 (4.21-13.46)
HDRS score	6.13 (5.07-7.18)	6.67 (6.15-7.19)	6.33 (3.29-9.38)

CI: Confidence Interval. FPG: Fasting Plasma Glucose. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. BMI: Body Mass Index. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. MADRS: Montgomery-Åsberg Depression Rating Scale. HDRS: Hamilton Depression Rating Scale.
*p = 0.054 tested by One-Way ANOVA.

Following the WHO recommended classification of adult underweight, overweight and obesity, the percentage distribution of BMI status of the study participants (total and by gender) is shown in the figure below:

Figure 3.1: Percentage Distribution of BMI Status in 713 Participants from Northeastern Brazil



3.2 DIABETES

3.2.1 Prevalence of DM, IFG, Isolated IFG, IGT and Isolated IGT

The overall prevalence of DM (new and pre-existing cases) was 16%. The total prevalence of diabetes increased significantly with higher age ($p < 0.001$), as well as the prevalence in males ($p = 0.041$) and females ($p < 0.001$). No significant difference was found between males and females (Table 3.4 and Figure 3.2).

Table 3.4: Prevalence of DM by Age and Gender in 714 Participants from Northeastern Brazil

	Male		Female		Total	
Age (years)	**n**	**Prevalence of DM**	**n**	**Prevalence of DM**	**n**	**Prevalence of DM**
		% (95% CI)		*% (95% CI)*		*% (95% CI)*
20-35	76	5.3 (2.0-13.3)*	159	6.9 (3.9-12.1)**	235	6.4 (3.9-10.3)**
36-50	78	15.4 (8.9-25.3)	163	17.2 (12.1-23.8)	241	16.6 (12.4-21.9)
≥ 51	88	18.2 (11.4-27.8)	150	28.7 (22.0-36.5)	238	24.8 (19.7-30.7)
Total	242	13.2 (9.5-18.1)	472	17.4 (14.2-21.1)	714	16.0 (13.5-18.8)

CI: Confidence Interval. DM: Diabetes Mellitus.
*p<0.05 or **p<0.01 by using Chi-square test for variation among the age categories.

A substantial agreement between FPG and 2-h values in the 75-g Oral Glucose Tolerance Test (OGTT) was found when diagnosing DM (Kappa = 0.74, p < 0.001) (Table 3.5).

Table 3.5: Agreement between FPG and OGTT in Diagnosing DM

		Diabetes according to OGTT		
		No Diabetes	Diabetes	Total
Diabetes according to FPG	No Diabetes	598	20	618
	Diabetes	22	72	94
	Total	620	92	712

FPG: Fasting Plasma Glucose. OGTT: Oral Glucose Tolerance Test. DM: Diabetes Mellitus.

The overall prevalence of IFG and isolated IFG were 5.8 and 4.2%, respectively. The prevalence of isolated IFG was significantly higher among females compared to males (p = 0.042). No significant difference was observed with regard to the prevalence of IFG by gender (Table 3.6 and Figure 3.2).

Table 3.6: Prevalence of IFG and Isolated IFG by Age and Gender in Study Subjects from Northeastern Brazil

Age (years)	Prevalence of IFG			Prevalence of Isolated IFG		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
	% (95% CI)	*% (95% CI)*	*% (95% CI)*	*% (95% CI)*	*% (95% CI)*	*% (95% CI)*
20-35	2.7 (0.7-10.2)	8.2 (4.8-13.6)	6.4 (3.9-10.4)	1.3 (0.2-9.0)	7.0 (3.9-12.2)	5.2 (2.9-8.9)
36-50	3.8 (1.2-11.4)	3.7 (1.7-8.0)	3.7 (1.9-7.0)	2.6 (0.6-9.8)	3.1 (1.3-7.2)	2.9 (1.4-6.0)
≥ 51	4.5 (1.7-11.6)	8.7 (5.1-14.4)	7.1 (4.5-11.2)	2.3 (0.6-8.8)	6.0 (3.1-11.2)	4.6 (2.6-8.2)
Total	3.7 (1.9-7.1)	6.8 (4.8-9.4)	5.8 (4.3-7.7)	2.1 (0.9-4.9)	5.3 (3.6-7.7)*	4.2 (3.0-6.0)

CI: Confidence Interval. IFG: Impaired Fasting Glucose.
*p<0.05 by using Chi-square test between males and females.

The overall prevalence of IGT and isolated IGT were 11.8% and 8.8%, respectively. The total prevalence of IGT (p = 0.020) and the prevalence of IGT in males (p = 0.019) increased significantly with higher age. Furthermore, the total prevalence of isolated IGT showed a borderline non-significant increase with higher age (p = 0.058). Among males, the prevalence of isolated IGT increased significantly with higher age (p = 0.009). No significant difference was found between males and females with regard either to the prevalence of IGT or isolated IGT (Table 3.7 and Figure 3.2).

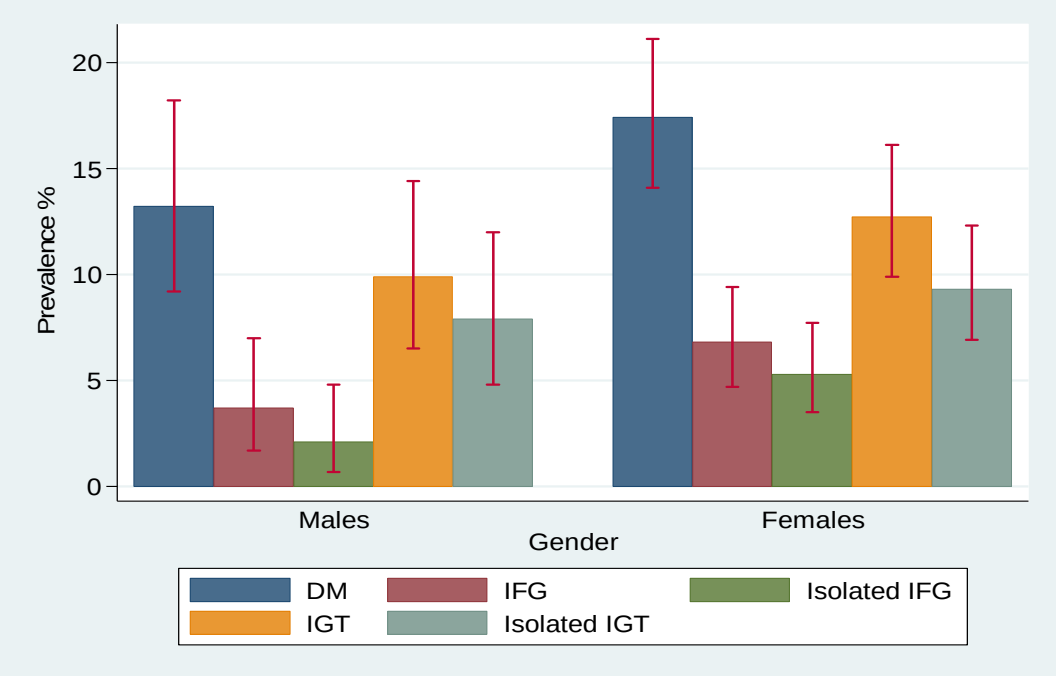
Table 3.7: Prevalence of IGT and Isolated IGT by Age and Gender in Study Subjects from Northeastern Brazil

Age (yrs)	Prevalence of IGT			Prevalence of Isolated IGT		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
	% (95% CI)	*% (95% CI)*	*% (95% CI)*	*% (95% CI)*	*% (95% CI)*	*% (95% CI)*
20-35	5.3 (2.0-13.3)*	8.9 (5.3-14.4)	7.7 (4.9-11.9)*	2.7 (0.7-10.2)**	7.6 (4.3-12.9)	6.0 (3.6-9.9)†
36-50	6.4 (2.7-14.6)	14.1 (9.5-20.4)	11.6 (8.1-16.3)	5.1 (1.9-13.0)	9.8 (6.1-15.5)	8.3 (5.4-12.5)
≥ 51	17.0 (10.5-26.5)	15.3 (10.4-22.1)	16.0 (11.8-21.2)	14.8 (8.7-23.9)	10.7 (6.6-16.7)	12.2 (8.6-17.0)

Total	9.9 (6.7-14.4)	12.7 (10.0-16.1)	11.8 (9.6-14.4)	7.9 (5.1-12.1)	9.3 (7.0-12.3)	8.8 (7.0-11.2)

IGT: Impaired Glucose Tolerance. CI: Confidence Interval.
*p<0.05 or **p<0.01 by using Chi-square test for variation among the age categories.
†p=0.058 by using Chi-square test for variation among the age categories.

Figure 3.2: Prevalence of DM, IFG, Isolated IFG, IGT and Isolated IGT by Gender in Study Subjects from Northeastern Brazil



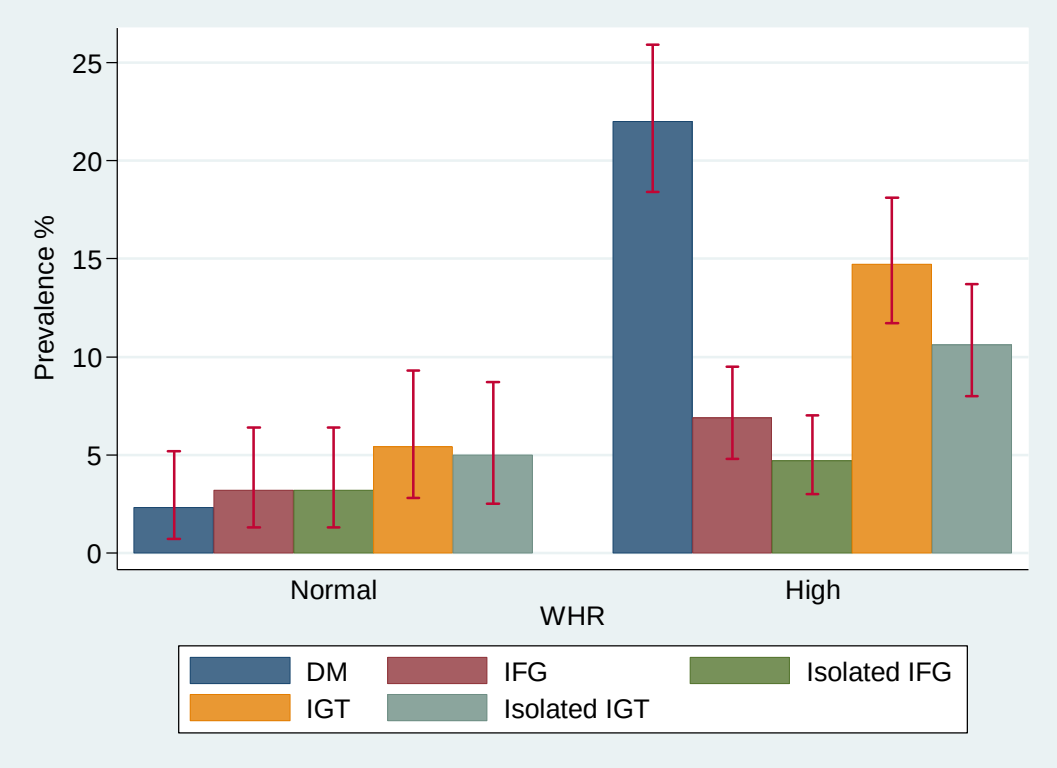
The prevalence of DM was significantly higher among those with family history of DM (p<0.001) and high WHR (p<0.001) (Table 3.8 and Figure 3.3). Furthermore, the prevalence of DM increased significantly with higher BMI (p<0.001), lower amounts of physical activity (p<0.001) and lower levels of education (p<0.001), although slight insignificant decrease was observed for the "high school" stratum (Table 3.8). The prevalence of IFG (p=0.046) and IGT (p<0.001) were significantly higher among those with high WHR (Table 3.8 and Figure 3.3). Additionally, the prevalence of IGT increased significantly with lower amounts of physical activity (p=0.035) and higher BMI (p=0.016), although slight insignificant decrease was observed for the "normal" BMI stratum. Furthermore, the prevalence of IGT was significantly higher among those who were previous smokers compared to current smokers (p=0.009) (Table 3.8).

Table 3.8: Prevalence of DM, IFG and IGT by Selected Socio-Demographic / Behavioural and Clinical Variables in Study Subjects from Northeastern Brazil

	n	Diabetes % (95% CI)	n	IFG % (95% CI)	n	IGT % (95% CI)
Ethnicity						
White	120	12.5 (7.7-19.8)	120	3.3 (1.2-8.6)	120	16.7 (11.0-24.5)
Brown	576	17.0 (14.2-20.3)	575	6.3 (4.5-8.6)	575	10.8 (8.5-13.6)
Black	18	5.6 (0.7-32.0)	18	5.6 (0.7-32.0)	18	11.1 (2.7-36.3)
Monthly Income						
Low (≤ 1MW)	445	16.0 (12.8-19.7)	445	5.2 (3.5-7.7)	444	11.5 (8.8-14.8)
Middle (1MW - 5MW)	262	16.0 (12.1-21.0)	261	6.9 (4.4-10.7)	262	12.2 (8.8-16.8)
High (≥ 5MW)	5	20.0 (2.1-74.4)	5	0	5	20.0 (2.1-74.4)
Education						
University or Higher	28	10.7 (3.4-28.9)**	28	10.7 (3.4-28.9)	28	14.3 (5.4-32.9)
High School	178	5.6 (3.0-10.2)	177	3.4 (1.5-7.4)	178	7.3 (4.3-12.2)
Primary School	413	18.9 (15.4-23.0)	413	6.3 (4.3-9.1)	412	13.3 (10.4-17.0)
Illiterate	95	24.2 (16.6-33.9)	95	6.3 (2.8-13.4)	95	12.6 (7.3-21.0)
Family History DM						
No	429	10.0 (7.5-13.3)**	429	6.1 (4.2-8.8)	428	11.2 (8.5-14.6)
Yes	285	24.9 (20.2-30.3)	284	5.3 (3.2-8.6)	285	12.6 (9.2-17.0)
Physical Activity						
High	56	3.6 (0.9-13.4)**	56	1.8 (0.2-11.8)	56	5.4 (1.7-15.5)*
Moderate	184	6.5 (3.7-11.2)	183	3.3 (1.5-7.1)	184	8.2 (5.0-13.1)
Low	474	21.1 (17.6-25.0)	474	7.2 (5.2-9.9)	473	14.0 (11.1-17.4)
Smoking						
Never	428	14.5 (11.5-18.2)	428	5.4 (3.6-8.0)	428	11.9 (9.2-15.4)
Previous	147	19.7 (14.0-27.0)	147	7.5 (4.2-13.0)	146	16.4 (11.2-23.4)*
Current	139	16.5 (11.2-23.7)	138	5.1 (2.4-10.3)	139	6.5 (3.4-12.0)
BMI						
<18.5 (Underweight)	26	7.7 (1.9-26.7)**	26	3.8 (0.5-23.6)	26	11.5 (3.7-30.8)*
18.5-24.99 (Normal)	246	9.8 (6.6-14.2)	245	4.1 (2.2-7.4)	246	8.1 (5.3-12.3)
25-29.99 (Overweight)	266	15.0 (11.2-19.9)	266	6.0 (3.7-9.6)	265	10.9 (7.7-15.3)
≥30 (Obesity)	175	26.9 (20.8-33.9)	175	8.0 (4.8-13.1)	175	18.3 (13.2-24.7)
WHR						
Normal	221	2.3 (0.9-5.3)**	221	3.2 (1.5-6.5)*	221	5.4 (3.1-9.3)**
High	492	22.0 (18.5-25.8)	491	6.9 (5.0-9.5)	491	14.7 (11.8-18.1)

DM: Diabetes Mellitus. IFG: Impaired Fasting Glucose. IGT: Impaired Glucose Tolerance. CI: Confidence Interval. MW: Minimum. WHR: Waist-to-Hip Ratio.
Wage in 2012. BMI: Body Mass Index.
*p<0.05 or **p<0.01 by Chi-square test or Fisher's Exact test.

Figure 3.3: Prevalence of DM, IFG, Isolated IFG, IGT and Isolated IGT by WHR in Study Subjects from Northeastern Brazil



3.2.2 Characteristics of the Study Population with and without Diabetes

The mean age was significantly higher among those with diabetes compared to those without diabetes (53.3 vs. 43.6), while the mean years of education was significantly lower among those with diabetes (4.8 vs. 6.9). There was a significant difference between those with and without diabetes with regard to the amounts of physical activity ($p<0.001$). In addition, the alcohol consumption was significantly lower among those with diabetes. A positive family history of DM was more common among those with diabetes ($p<0.001$) (Table 3.9).

Table 3.9: Socio-Demographic / Behavioural Characteristics of 714 Subjects with or without Diabetes from Northeastern Brazil

	With Diabetes	Without Diabetes
n = 714	114	600
	Mean or % (95% CI)	*Mean or % (95% CI)*
Age (years)	53.3 (50.4-56.1)**	43.6 (42.3-44.8)

Gender		
Male	28.1% (20.6-37.1)	35.0% (31.3-38.9)
Female	71.9% (62.9-79.4)	65.0% (61.1-68.7)
Ethnicity		
White	13.1% (8.1-20.7)	17.5% (14.7-20.8)
Brown	86.0% (78.3-91.2)	79.7% (76.2-82.7)
Black	0.9% (0.1-6.0)	2.8% (1.8-4.5)
Monthly Income		
Low (≤ 1MW)	62.3% (53.0-70.7)	62.5% (58.6-66.3)
Middle (1MW - 5MW)	36.8% (28.5-46.1)	36.8% (33.0-40.7)
High (≥ 5MW)	0.9% (0.1-6.0)	0.7% (0.3-1.8)
Occupation		
Student	0%	1.5% (0.8-2.9)
Agriculture	2.6% (0.8-7.9)	6.2% (4.5-8.4)
Industry and Services	23.7% (16.7-32.4)	30.5% (26.9-34.3)
Domestic Labour	28.1% (20.6-37.1)	28.8% (25.3-32.6)
Construction	1.8% (0.4-6.8)	4.2% (2.8-6.1)
Sick Benefit	0.9% (0.1-6.0)	0.5% (0.2-1.5)
Retired	37.7% (29.3-47.0)	18.8% (15.9-22.2)
Unemployed	2.6% (0.8-7.9)	4.3% (3.0-6.3)
Other	2.6% (0.8-7.9)	5.2% (3.7-7.3)
Education (years)	4.8 (4.1-5.5)**	6.9 (6.5-7.3)
Physical Activity		
Low	87.7% (80.3-92.6)**	62.3% (58.4-66.1)
Moderate	10.5% (6.1-17.7)	28.7% (25.2-32.4)
High	1.8% (0.4-6.8)	9.0% (7.0-11.6)
Smoking		
Never	54.4% (45.1-63.3)	61.0% (57.0-64.8)
Previous	25.4% (18.3-34.3)	19.7% (16.7-23.1)
Current	20.2% (13.8-28.6)	19.3% (16.4-22.7)
Alcohol Consumption (yes)	26.3% (19.0-35.2)*	38.2% (34.4-42.1)
Family History DM (yes)	62.3% (53.0-70.7)**	35.7% (31.9-39.6)
Family History Depression (yes)	13.2% (8.1-20.7)	12.8% (10.4-15.8)

CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus.
*p<0.05 or **p<0.01 by using Chi-square test or Independent Samples T test.

FPG, 2-hour plasma glucose, capillary HbA1c, fasting insulin, total cholesterol, triglycerides, LDL-C, BMI, body fat percentage, WHR, SBP, DBP, MADRS and HDRS scores were significantly higher among those with diabetes compared to those without diabetes. The mean levels of HDL-C showed lower borderline significant level among those with diabetes (Table 3.10).

Table 3.10: Clinical Characteristics of 714 Subjects with or without Diabetes from Northeastern Brazil

	With Diabetes	Without Diabetes
n = 714	114	600
	Mean (95% CI)	*Mean (95% CI)*
FPG (mmol/l)	9.37 (8.53-10.20)**	4.74 (4.69-4.79)
2-hour Plasma Glucose (mmol/l)	15.69 (14.36-17.02)**	6.37 (6.27-6.47)
Capillary HbA1c (%)	8.07 (7.67-8.47)**	5.99 (5.94-6.03)
Fasting Cortisol (mcg/dl)	14.24 (13.23-15.26)	14.12 (13.72-14.53)
Fasting Insulin (micro UI/ml)	8.23 (6.88-9.58)*	6.49 (6.14-6.85)
Total Cholesterol (mmol/l)	5.14 (4.95-5.33)**	4.63 (4.55-4.71)
Triglycerides (mmol/l)	2.22 (1.85-2.59)**	1.42 (1.28-1.55)
HDL-C (mmol/l)	1.20 (1.18-1.23)†	1.23 (1.22-1.24)
LDL-C (mmol/l)	3.02 (2.84-3.20)*	2.83 (2.75-2.90)
BMI (Kg/m^2)	29.43 (28.33-30.52)**	26.38 (25.99-26.78)
Body Fat Percentage	36.61 (35.02-38.21)**	32.10 (31.36-32.80)
WHR	0.98 (0.96-1.00)**	0.90 (0.89-0.91)
SBP (mmHg)	138.81 (134.25-143.37)**	125.52 (123.71-127.32)
DBP (mmHg)	81.10 (78.73-83.47)**	75.96 (74.53-77.39)
MADRS score	10.41 (8.51-12.32)*	7.90 (7.25-8.56)
HDRS score	8.85 (7.44-10.27)**	6.14 (5.67-6.60)

CI: Confidence Interval. FPG: Fasting Plasma Glucose. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. BMI: Body Mass Index. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. MADRS: Montgomery-Åsberg Depression Rating Scale. HDRS: Hamilton Depression Rating Scale.
*p<0.05, **p<0.01 or †p = 0.051 by using Independent Samples T test.

3.2.3 Socio-Demographic / Behavioural and Clinical Factors Associated with Diabetes / Univariate and Multivariate Analyses

In order to identify the factors associated with diabetes, univariate and multivariate logistic regression models were used. Age, education level, amount of physical activity, alcohol consumption, family history of DM, BMI status, fasting insulin, total cholesterol, triglycerides, LDL-C, body fat percentage, WHR, SBP and DBP were found to be significant risk indicators for the occurrence of DM in univariate analysis. Monthly income, occupation and HDL-C were borderline non-significant indicators. Then, only those significant (and borderline non-significant) indicators were included in the multivariate regression model. Education level, family history of DM, triglycerides, body fat percentage, WHR, and DBP remained significant after controlling for potential confounding factors in the multivariate analysis. Of note, WHR was the prime indicator of diabetes in the study population. The risk

of developing diabetes was almost 6.4 times higher among those with a high WHR, compared to those with a normal value (Table 3.11).

Table 3.11: Univariate and Multivariate Regression Models for the Relationship between Diabetes and Selected Socio-Demographic / Behavioural and Clinical Variables in 714 Subjects from Northeastern Brazil

Variables	**n**	**OR (95% CI)[1]**	***p-value***	**OR (95% CI)[2]**	***p-value***
Socio-Demographic / Behavioural Variables					
Gender					
Male	242	1.00 (reference)			
Female	472	1.38 (0.89-2.15)	0.153		
Age groups (years)					
20-35	235	1.00		1.00	
36-50	241	2.92 (1.57-5.45)	**0.001**	1.27 (0.57-2.80)	0.556
≥ 51	238	4.83 (2.65-8.81)	< **0.001**	1.14 (0.48-2.70)	0.773
Ethnicity					
White	120	1.00			
Brown	576	1.44 (0.80-2.57)	0.225		
Black	18	0.41 (0.05-3.32)	0.405		
Education					
High School or Higher	206	1.00		1.00	
Primary School	413	4.74 (2.28-9.86)	< **0.001**	4.54 (1.58-13.08)	**0.005**
Illiterate	95	3.46 (1.87-6.38)	< **0.001**	2.70 (1.16-6.28)	**0.021**
Monthly Income					
< 2MW	641	1.00		1.00	
≥ 2MW	71	1.77 (0.98-3.17)	**0.057**	1.64 (0.67-4.03)	0.283
Occupation					
Manual Labor	67	1.00		1.00	
Not Manual Labor	647	2.51 (0.99-6.39)	**0.053**	0.98 (0.29-3.37)	0.973
Physical Activity					
High	56	1.00		1.00	
Moderate	184	7.22 (1.73-30.12)	**0.007**	2.75 (0.56-13.49)	0.213
Low	474	1.88 (0.41-8.68)	0.417	0.83 (0.15-4.57)	0.830
Smoking					
Never	428	1.00			
Previous	147	1.45 (0.89-2.36)	0.134		
Current	139	1.17 (0.69-1.97)	0.555		
Alcohol Consumption					
No	455	1.00		1.00	
≤ 4 times a month	243	0.60 (0.38-0.94)	**0.027**	0.78 (0.43-1.44)	0.434

> 4 times a month	16	0.29 (0.04-2.26)	0.240	0.25 (0.02-2.77)	0.256
Family History DM					
No	429	1.00		1.00	
Yes	285	2.98 (1.97-4.51)	< **0.001**	3.14 (1.86-5.28)	< **0.001**
Family History Depression					
No	622	1.00			
Yes	92	1.03 (0.57-1.86)	0.924		
Clinical Variables					
BMI Status					
< 25	272	1.00		1.00	
25-29.99	266	1.68 (0.99-2.83)	**0.055**	0.52 (0.25-1.06)	0.073
≥30	175	3.47 (2.06-5.87)	< **0.001**	0.69 (0.29-1.69)	0.419
Fasting Cortisol (mcg/dl)					
Low (<6.7)	31	1.00			
Normal (6.7 - 22.6)	630	1.26 (0.43-3.68)	0.674		
High (≥ 22.6)	48	1.78 (0.50-6.26)	0.372		
Fasting Insulin (micro UI/ml)	703	1.06 (1.02-1.10)	**0.002**	0.99 (0.94-1.04)	0.686
Total Cholesterol (mmol/l)					
Desirable (< 5.2)	506	1.00		1.00	
Borderline High (5.2 - 6.2)	141	2.23 (1.40-3.57)	**0.001**	1.72 (0.72-4.13)	0.224
High (≥ 6.2)	61	2.29 (1.21-4.35)	**0.011**	1.58 (0.32-7.80)	0.575
Triglycerides (mmol/l)					
Desirable (< 1.7)	538	1.00		1.00	
Borderline High (1.7 - 2.3)	76	2.38 (1.32-4.30)	**0.004**	1.80 (0.85-3.79)	0.123
High (≥ 2.3)	95	4.28 (2.61-7.03)	< **0.001**	3.47 (1.61-7.46)	**0.001**
HDL-C (mmol/l)	713	0.20 (0.04-1.01)	**0.051**	0.17 (0.02-1.38)	0.097
LDL-C (mmol/l)					
Desirable (< 3.4)	512	1.00		1.00	
Borderline High (3.4 - 4.1)	97	1.93 (1.14-3.28)	**0.015**	1.32 (0.52-3.32)	0.561
High (≥ 4.1)	70	1.16 (0.58-2.31)	0.677	0.37 (0.08-1.64)	0.191
Body Fat Percentage	698	1.07 (1.04-1.09)	< **0.001**	1.06 (1.01-1.10)	**0.014**
WHR					
Normal	221	1.00		1.00	
High	492	12.15 (4.88-30.24)	< **0.001**	6.38 (2.13-19.07)	**0.001**
SBP (mmHg)					
< 140	537	1.00		1.00	
≥ 140	175	2.35 (1.54-3.58)	< **0.001**	0.97 (0.47-1.98)	0.929
DBP (mmHg)					
< 90	631	1.00		1.00	
≥ 90	81	3.58 (2.15-5.96)	< **0.001**	2.56 (1.20-5.46)	**0.015**

OR: Odds Ratio. CI: Confidence Interval. MW: Brazilian Minimum Wage in 2012. DM: Diabetes Mellitus. BMI: Body Mass Index.

HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure.
1: Crude OR; 2: Adjusted OR for age, education, monthly income, occupation, physical activity, alcohol consumption, family history of diabetes, BMI status, fasting insulin, total cholesterol, triglycerides, HDL-C, LDL-C, body fat percentage, WHR, SBP and DBP.

3.3 DEPRESSION

3.3.1 Prevalence of Depression According to MADRS and HDRS

Initially, it is to be noted that those with a known diagnosis of depression were considered depressed, irrespective of the depressive scores obtained either with MADRS or HDRS.

When the MADRS was applied, the overall prevalence of depression (new and pre-existing cases) was 15%. Among women, the prevalence of depression increased significantly with higher age (p=0.032). Moreover, the total prevalence of depression was significantly higher among women compared to men (p<0.001) (Table 3.12).

Table 3.12: Prevalence of Depression (MADRS ≥ 20) by Age and Gender in 713 Participants from Northeastern Brazil

	Male		Female		Total	
Age (years)	**n**	**Prevalence of Depression**	**n**	**Prevalence of Depression**	**n**	**Prevalence of Depression**
		% (95% CI)		*% (95% CI)*		*% (95% CI)*
20-35	76	7.9 (3.6-16.6)	158	15.2 (10.4-21.7)*	234	12.8 (9.1-17.8)
36-50	78	6.4 (2.7-14.6)	163	16.6 (11.6-23.1)	241	13.3 (9.5-18.2)
≥ 51	88	6.8 (3.1-14.5)	150	26.0 (19.6-33.6)	238	18.9 (14.4-24.4)
Total	242	7.0 (4.4-11.0)	471	19.1 (15.8-22.9)**	713	15.0 (12.6-17.8)

MADRS: Montgomery-Åsberg Depression Rating Scale. CI: Confidence Interval.
*p<0.05 by using Chi-square test for variation among the age categories.
**p<0.01 tested by Chi-square test between men and women.

When using the HDRS, the overall prevalence of depression (new and pre-existing cases) was 15.5%. No significant difference was observed for the prevalence of depression in

age specific strata. However, the total prevalence of depression was significantly higher among women compared to men (p<0.001) (Table 3.13).

Table 3.13: Prevalence of Depression (HDRS ≥ 14) by Age and Gender in 714 Participants from Northeastern Brazil

	Male		Female		Total	
Age (years)	**n**	**Prevalence of Depression**	**n**	**Prevalence of Depression**	**n**	**Prevalence of Depression**
		% (95% CI)		*% (95% CI)*		*% (95% CI)*
20-35	76	9.2 (4.4-18.2)	159	16.4 (11.4-23.0)	235	14.0 (10.1-19.1)
36-50	78	7.7 (3.5-16.2)	163	18.4 (13.2-25.1)	241	14.9 (11.0-20.0)
≥ 51	88	8.0 (3.8-15.9)	150	23.3 (17.2-30.8)	238	17.6 (13.3-23.0)
Total	242	8.3 (5.4-12.5)	472	19.3 (16.0-23.1)**	714	15.5 (13.1-18.4)

HDRS: Hamilton Depression Rating Scale. CI: Confidence Interval.
**p<0.01 tested by Chi-square test between men and women.

According to MADRS and HDRS, the prevalence of depression decreased significantly with higher BMI, although slight insignificant increase was observed for the group with "obesity". Also according to both the scales, the prevalence of depression increased significantly with family history of depression, smoking habits and lower income. Only according to HDRS, those with an education level of "primary school" had a significantly higher prevalence of depression compared to those with a "high school" level (Table 3.14).

Table 3.14: Prevalence of Depression According to MADRS and HDRS by Selected Socio-Demographic / Behavioural and Clinical Variables in Study Participants from Northeastern Brazil

	n	Depression - MADRS ≥ 20 % (95% CI)	n	Depression - HDRS ≥ 14 % (95% CI)
Ethnicity				
White	120	11.7 (7.0-18.8)	120	11.7 (7.0-18.8)
Brown	575	15.7 (12.9-18.9)	576	16.5 (13.7-19.8)
Black	18	16.7 (5.3-41.8)	18	11.1 (2.7-36.3)

Monthly Income				
High (≥ 5MW)	5	0*	5	0**
Middle (1MW - 5MW)	262	10.3 (7.2-14.6)	262	10.3 (7.2-14.6)
Low (≤ 1MW)	444	18.0 (14.7-21.9)	445	18.9 (15.5-22.8)
Education				
University or Higher	28	3.6 (0.5-22.1)	28	3.6 (0.5-22.1)
High School	178	12.4 (8.3-18.1)	178	11.8 (7.8-17.4)*
Primary School	412	17.2 (13.9-21.2)	413	18.6 (15.2-22.7)
Illiterate	95	13.7 (8.1-22.2)	95	12.6 (7.3-21.0)
Marital Status				
Single	159	16.4 (11.4-23.0)	159	17.0 (11.9-23.7)
Married / Cohabitant	476	13.4 (10.7-16.8)	477	14.0 (11.2-17.5)
Divorced / Separated	28	17.9 (7.5-36.8)	28	14.3 (5.4-32.9)
Widow(er)	49	24.5 (14.4-38.5)	49	26.5 (16.0-40.7)
Family History Depression				
No	621	12.9 (10.5-15.8)**	622	13.3 (10.9-16.3)**
Yes	92	29.3 (20.9-39.5)	92	30.4 (21.9-40.6)
BMI				
<18.5 (Underweight)	26	34.6 (18.8-54.7)*	26	34.6 (18.8-54.7)*
18.5-24.99 (Normal)	246	13.8 (10.0-18.7)	246	14.6 (10.7-19.6)
25-29.99 (Overweight)	265	12.8 (9.3-17.4)	266	13.9 (10.2-18.6)
≥30 (Obesity)	175	16.6 (11.7-22.9)	175	16.6 (11.7-22.9)
Physical Activity				
High	56	14.3 (7.3-26.2)	56	14.3 (7.3-26.2)
Moderate	184	12.5 (8.4-18.1)	184	13.0 (8.9-18.8)
Low	473	16.1 (13.0-19.7)	474	16.7 (13.6-20.3)
Smoking				
Never	428	11.9 (9.2-15.4)**	428	13.1 (10.2-16.6)*
Previous	146	15.8 (10.7-22.6)	147	15.6 (10.6-22.5)
Current	139	23.7 (17.4-31.6)	139	23.0 (16.7-30.8)

MADRS: Montgomery-Åsberg Depression Rating Scale. HDRS: Hamilton Depression Rating Scale. CI: Confidence Interval. MW: Minimum Wage in 2012. BMI: Body Mass Index.
*p< 0.05 or **p<0.01 by Chi-square test or Fisher's Exact test.

3.3.2 Characteristics of the Study Population with and without Depression

When MADRS was used, it was found that the proportion of women was significantly higher among those with depression compared to those without depression (p<0.001). There was also a significant difference between those with and without depression with regard to the monthly income levels (p=0.019) and smoking habits (p=0.003). The alcohol consumption was significantly lower among those classified as depressed (p=0.019).

Furthermore, a positive family history of depression was more common among those with depression (p<0.001) (Table 3.15).

Table 3.15: Socio-Demographic / Behavioural Characteristics of 713 Subjects with or without Depression According to MADRS from Northeastern Brazil

	With Depression MADRS ≥ 20	**Without Depression MADRS < 20**
n = 713	107	606
	Mean or % (95% CI)	*Mean or % (95% CI)*
Age (years)	47.3 (44.3-50.4)	44.8 (43.5-46.0)
Gender		
Male	15.9% (10.1-24.1)**	37.1% (33.4-41.1)
Female	84.1% (75.9-89.9)	62.9% (58.9-66.6)
Ethnicity		
White	13.1% (7.9-20.9)	17.5% (14.7-20.7)
Brown	84.1% (75.9-89.9)	80.0% (76.7-83.0)
Black	2.8% (0.9-8.4)	2.5% (1.5-4.1)
Monthly Income		
Low (≤ 1MW)	74.8% (65.6-82.1)*	60.3% (56.3-64.1)
Middle (1MW - 5MW)	25.2% (17.9-34.4)	38.9% (35.1-42.9)
High (≥ 5MW)	0%	0.8% (0.3-2.0)
Occupation		
Student	0.9% (0.1-6.4)	1.3% (0.7-2.6)
Agriculture	3.7% (1.4-9.6)	5.9% (4.3-8.1)
Industry and Services	23.4% (16.3-32.4)	30.4% (26.8-34.2)
Domestic Labour	35.5% (27.0-45.1)	27.6% (24.1-31.3)
Construction	0%	4.5% (3.1-6.4)
Sick Benefit	1.9% (0.5-7.2)	0.3% (0.1-1.3)
Retired	26.2% (18.7-35.4)	21.1% (18.0-24.6)
Unemployed	5.6% (2.5-12.0)	3.8% (2.5-5.7)
Other	2.8% (0.9-8.4)	5.1% (3.6-7.2)
Education (years of study)	6.1 (5.4-6.9)	6.6 (6.3-7.0)
Marital Status		
Single	24.3% (17.1-33.4)	22.0% (18.9-25.5)
Married / Cohabitant	59.8% (50.2-68.7)	68.1% (64.3-71.7)
Divorced / Separated	4.7% (1.9-10.8)	3.8% (2.5-5.7)
Widow(er)	11.2% (6.5-18.8)	6.1% (4.5-8.3)
Physical Activity		
Low	71.0% (61.7-78.9)	65.5% (61.6-69.2)
Moderate	21.5% (14.7-30.3)	26.6% (23.2-30.2)
High	7.5% (3.8-14.3)	7.9% (6.0-10.4)

Smoking		
Never	47.7% (38.3-57.2)**	62.2% (58.3-66.0)
Previous	21.5% (14.7-30.3)	20.3% (17.3-23.7)
Current	30.8% (22.8-40.3)	17.5% (14.7-20.7)
Alcohol Consumption (yes)	26.2% (18.7-35.4)*	38.0% (34.2-41.9)
Family History DM (yes)	43.9% (34.8-53.5)	39.3% (35.5-43.2)
Family History Depression (yes)	25.2% (17.9-34.4)**	10.7% (8.5-13.5)

MADRS: Montgomery-Åsberg Depression Rating Scale. CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus.
*p< 0.05 or **p<0.01 by Chi-square test or Fisher's Exact test.

FPG, 2-hour Plasma Glucose, capillary HbA1c, body fat percentage, MADRS and HDRS scores were significantly higher among those classified as depressed (MADRS ≥ 20) (Table 3.16).

Table 3.16: Clinical Characteristics of 713 Subjects with or without Depression According to MADRS from Northeastern Brazil

	With Depression MADRS ≥ 20	**Without Depression MADRS < 20**
n = 713	107	606
	Mean (95% CI)	*Mean (95% CI)*
FPG (mmol/l)	6.17 (5.46-6.87)*	5.36 (5.18-5.54)
2-hour Plasma Glucose (mmol/l)	9.49 (8.21-10.77)**	7.57 (7.25-7.89)
Capillary HbA1c (%)	6.70 (6.36-7.04)*	6.25 (6.16-6.33)
Fasting Cortisol (mcg/dl)	13.09 (12.17-14.00)	14.32 (13.91-14.74)
Fasting Insulin (micro UI/ml)	7.24 (6.32-8.16)	6.69 (6.29-7.10)
Total Cholesterol (mmol/l)	4.87 (4.68-5.06)	4.69 (4.61-4.77)
Triglycerides (mmol/l)	1.57 (1.36-1.79)	1.54 (1.40-1.69)
HDL-C (mmol/l)	1.22 (1.20-1.25)	1.22 (1.21-1.23)
LDL-C (mmol/l)	2.94 (2.78-3.11)	2.84 (2.77-2.92)
BMI (Kg/m^2)	27.04 (25.83-28.24)	26.83 (26.44-27.23)
Body Fat Percentage	35.24 (33.49-36.99)**	32.36 (31.64-33.08)
WHR	0.92 (0.90-0.94)	0.92 (0.91-0.92)
SBP (mmHg)	125.49 (121.17-129.81)	128.03 (126.15-129.90)
DBP (mmHg)	75.23 (73.31-77.16)	77.03 (75.58-78.48)
MADRS score	24.27 (22.76-25.78)**	5.49 (5.11-5.86)
HDRS score	17.58 (16.35-18.81)**	4.63 (4.34-4.92)

MADRS: Montgomery-Åsberg Depression Rating Scale. CI: Confidence Interval. FPG: Fasting Plasma Glucose. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. BMI: Body Mass Index. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. HDRS: Hamilton Depression Rating Scale.
*p<0.05 or **p<0.01 by using Independent Samples T test.

Similarly to our previous findings, according to HDRS, the proportion of women was significantly higher among those classified as depressed (p<0.001). There was a significant difference between those with and without depression with regard to the monthly income levels (p=0.008) and smoking habits (p=0.019). The alcohol consumption was significantly lower among those with depression (p=0.047). Furthermore, a positive family history of depression was more common among those who were depressed (p<0.001) (Table 3.17).

Table 3.17: Socio-Demographic / Behavioural Characteristics of 714 Subjects with or without Depression According to HDRS from Northeastern Brazil

	With Depression HDRS ≥ 14	**Without Depression HDRS < 14**
n = 714	111	603
	Mean or % (95% CI)	*Mean or % (95% CI)*
Age (years)	46.1 (43.1-49.1)	44.9 (43.6-46.2)
Gender		
Male	18.0% (11.9-26.3)**	36.8% (33.0-40.8)
Female	82.0% (73.7-88.1)	63.2% (59.2-67.0)
Ethnicity		
White	12.6% (7.6-20.2)	17.6% (14.7-20.8)
Brown	85.6% (77.7-91.0)	79.8% (76.4-82.8)
Black	1.8% (0.4-7.0)	2.6% (1.6-4.3)
Monthly Income		
Low (≤ 1MW)	75.7% (66.8-82.8)**	60.1% (56.1-63.9)
Middle (1MW - 5MW)	24.3% (17.2-33.2)	39.1% (35.3-43.1)
High (≥ 5MW)	0%	0.8% (0.3-2.0)
Occupation		
Student	0.9% (0.1-6.2)	1.3% (0.7-2.6)
Agriculture	3.6% (1.4-9.3)	6.0% (4.3-8.2)
Industry and Services	25.2% (18.0-34.2)	30.2% (26.6-34.0)
Domestic Labour	36.0% (27.6-45.4)	27.4% (23.9-31.1)
Construction	0%	4.5% (3.1-6.5)
Sick Benefit	0.9% (0.1-6.2)	0.5% (0.2-1.5)
Retired	24.4% (17.2-33.2)	21.4% (18.3-24.9)
Unemployed	7.2% (3.6-13.8)	3.5% (2.3-5.3)
Other	1.8% (0.4-7.0)	5.2% (3.8-7.4)
Education (years of study)	6.2 (5.4-6.9)	6.6 (6.3-7.0)
Marital Status		
Single	24.3% (17.2-33.2)	21.9% (18.8-25.4)
Married / Cohabitant	60.4% (50.9-69.1)	68.1% (64.3-71.7)
Divorced / Separated	3.6% (1.4-9.3)	4.0% (2.7-5.9)
Widow(er)	11.7% (6.9-19.2)	6.0% (4.3-8.2)

Physical Activity		
Low	71.2% (62.0-78.9)	65.5% (61.6-69.2)
Moderate	21.6% (14.9-30.3)	26.5% (23.2-30.2)
High	7.2% (3.6-13.8)	8.0% (6.0-10.4)
Smoking		
Never	50.5% (41.2-59.7)*	61.7% (57.7-65.5)
Previous	20.7% (14.1-29.3)	20.6% (17.5-24.0)
Current	28.8% (21.1-38.0)	17.7% (14.9-21.0)
Alcohol Consumption (yes)	27.9% (20.3-37.0)*	37.8% (34.0-41.8)
Family History DM (yes)	44.1% (35.2-53.5)	39.1% (35.3-43.1)
Family History Depression (yes)	25.2% (18.0-34.2)**	10.6% (8.4-13.3)

HDRS: Hamilton Depression Rating Scale. CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus.
*p< 0.05 or **p<0.01 by Chi-square test or Fisher's Exact test.

Furthermore, 2-hour Plasma Glucose, capillary HbA1c, body fat percentage, MADRS and HDRS scores were significantly higher among those classified as depressed according to HDRS (Table 3.18).

Table 3.18: Clinical Characteristics of 714 Subjects with or without Depression According to HDRS from Northeastern Brazil

	With Depression HDRS ≥ 14	**Without Depression HDRS < 14**
n = 714	111	603
	Mean (95% CI)	*Mean (95% CI)*
FPG (mmol/l)	5.99 (5.38-6.60)	5.39 (5.20-5.58)
2-hour Plasma Glucose (mmol/l)	9.09 (7.96-10.22)*	7.63 (7.29-7.97)
Capillary HbA1c (%)	6.61 (6.28-6.93)*	6.26 (6.17-6.35)
Fasting Cortisol (mcg/dl)	13.30 (12.34-14.26)	14.30 (13.89-14.71)
Fasting Insulin (micro UI/ml)	7.10 (6.20-7.99)	6.71 (6.31-7.12)
Total Cholesterol (mmol/l)	4.86 (4.67-5.04)	4.68 (4.60-4.76)
Triglycerides (mmol/l)	1.60 (1.37-1.84)	1.54 (1.39-1.68)
HDL-C (mmol/l)	1.23 (1.20-1.25)	1.22 (1.21-1.23)
LDL-C (mmol/l)	2.94 (2.78-3.09)	2.84 (2.77-2.92)
BMI (Kg/m^2)	26.71 (25.57-27.85)	26.89 (26.49-27.30)
Body Fat Percentage	34.37 (32.66-36.08)*	32.49 (31.77-33.22)
WHR	0.916 (0.89-0.94)	0.915 (0.91-0.92)
SBP (mmHg)	124.08 (119.94-128.22)	128.30 (126.42-130.19)
DBP (mmHg)	75.13 (73.13-77.12)	77.09 (75.64-78.54)
MADRS score	23.23 (21.62-24.85)**	5.55 (5.16-5.95)
HDRS score	17.95 (16.82-19.08)**	4.48 (4.21-4.74)

HDRS: Hamilton Depression Rating Scale. CI: Confidence Interval. FPG: Fasting Plasma Glucose. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. BMI: Body Mass Index. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. MADRS: Montgomery-Åsberg Depression Rating Scale.
*p<0.05 or **p<0.01 by using Independent Samples T test.

3.3.3 Socio-Demographic / Behavioural and Clinical Factors Associated with Depression / Univariate and Multivariate Analyses

Univariate and multivariate logistic regression analyses were used to identify the independent risk indicators for depression assessed by MADRS and HDRS (Tables 3.19 and 3.20). According to MADRS, the significant risk indicators for the occurrence of depression in univariate analysis were gender, education level, monthly income, occupation, smoking, alcohol consumption, family history of depression and body fat percentage. Those significant variables were further used to perform a multivariate analysis. Only gender, smoking and family history of depression remained significant after the adjustment for the potential confounding factors. Being female, current smoker, and having a family history of depression were found to increase the risk for developing depression by 2.45, 2.53 and 2.92 times respectively (Table 3.19).

Table 3.19: Univariate and Multivariate Regression Models for the Relationship between Depression (MADRS ≥ 20) and Selected Socio-Demographic / Behavioural and Clinical Variables in 713 subjects from Northeastern Brazil

Variables	**n**	**OR (95% CI)[1]**	***p-value***	**OR (95% CI)[2]**	***p-value***
Socio-Demographic / Behavioural Variables					
Gender					
Male	242	1.00 (reference)		1.00	
Female	471	3.13 (1.82-5.39)	< **0.001**	2.45 (1.17-5.11)	**0.017**
Age groups (years)					
20-35	234	1.00			
36-50	241	1.04 (0.61-1.78)	0.882		
≥ 51	238	1.59 (0.96-2.62)	0.072		
Ethnicity					
White	120	1.00			
Brown	575	1.41 (0.77-2.56)	0.267		
Black	18	1.51 (0.39-5.90)	0.550		

Education					
High School or Higher	206	1.00		1.00	
Primary School	412	1.26 (0.61-2.61)	0.532	1.01 (0.45-2.29)	0.974
Illiterate	95	1.66 (1.001-2.74)	**0.049**	1.13 (0.64-1.98)	0.674
Marital Status					
Single	159	1.00			
Married / Cohabitant	476	0.80 (0.48-1.31)	0.364		
Divorced / Separated	28	1.11 (0.39-3.19)	0.844		
Widow(er)	49	1.66 (0.76-3.60)	0.200		
Monthly Income					
≥ 2MW	71	1.00		1.00	
< 2MW	640	3.21 (1.15-9.01)	**0.026**	1.92 (0.65-5.67)	0.241
Occupation					
Manual Labor	67	1.00		1.00	
Not Manual Labor	646	2.99 (1.06-8.39)	**0.038**	1.43 (0.45-4.59)	0.546
Physical Activity					
High	56	1.00			
Moderate	184	1.15 (0.52-2.53)	0.730		
Low	473	0.86 (0.36-2.04)	0.727		
Smoking					
Never	428	1.00		1.00	
Previous	146	1.38 (0.81-2.36)	0.234	1.65 (0.92-2.98)	0.094
Current	139	2.30 (1.41-3.75)	**0.001**	2.53 (1.44-4.44)	**0.001**
Alcohol Consumption					
No	455	1.00		1.00	
≤ 4 times a month	242	0.55 (0.34-0.89)	**0.014**	0.76 (0.45-1.28)	0.303
> 4 times a month	16	1.10 (0.31-3.95)	0.886	1.16 (0.29-4.61)	0.835
Family History DM					
No	428	1.00			
Yes	285	1.21 (0.80-1.83)	0.366		
Family History Depression					
No	621	1.00		1.00	
Yes	92	2.81 (1.69-4.66)	**< 0.001**	2.92 (1.70-5.01)	**< 0.001**
Clinical Variables					
BMI (Kg/m^2)					
< 25	272	1.00			
25-29.99	265	0.78 (0.48-1.27)	0.326		
≥30	175	1.06 (0.63-1.77)	0.830		
Fasting Cortisol					
Low (<6.7)	31	1.00			
Normal (6.7 - 22.6)	629	0.60 (0.25-1.44)	0.254		
High (≥ 22.6)	48	0.31 (0.08-1.17)	0.085		
Fasting Insulin (micro UI/ml)	702	1.02 (0.98-1.06)	0.306		

Total Cholesterol (mmol/l)					
Desirable (< 5.2)	505	1.00			
Borderline High (5.2 - 6.2)	141	1.42 (0.87-2.32)	0.155		
High (≥ 6.2)	61	0.78 (0.34-1.78)	0.555		
Triglycerides (mmol/l)					
Desirable (< 1.7)	537	1.00			
Borderline High (1.7 - 2.3)	76	1.29 (0.68-2.46)	0.438		
High (≥ 2.3)	95	1.56 (0.89-2.74)	0.117		
HDL-C (mmol/l)	712	0.97 (0.18-5.26)	0.972		
LDL-C (mmol/l)					
Desirable (< 3.4)	511	1.00			
Borderline High (3.4 - 4.1)	97	1.15 (0.64-2.07)	0.646		
High (≥ 4.1)	70	0.97 (0.48-1.98)	0.931		
Body Fat Percentage	697	1.04 (1.01-1.07)	**0.003**	1.01 (0.98-1.04)	0.614
WHR					
Normal	221	1.00			
High	491	1.05 (0.67-1.64)	0.837		

MADRS: Montgomery-Åsberg Depression Rating Scale. OR: Odds Ratio. CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus. BMI: Body Mass Index. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. WHR: Waist-to-Hip Ratio.
1: Crude OR; 2: Adjusted OR for gender, education, monthly income, occupation, smoking, alcohol consumption, family history of depression and body fat percentage.

Similarly, according to HDRS, gender, education, monthly income, occupation, smoking, alcohol consumption, family history of depression, and body fat percentage were found to be significant indicators in univariate analysis. In multivariate analysis, only gender, smoking and family history of depression remained significant after adjusting for the potential confounding factors (Table 3.20).

Table 3.20: Univariate and Multivariate Regression Models for the Relationship between Depression (HDRS ≥ 14) and Selected Socio-Demographic / Behavioural and Clinical Variables in 714 Subjects from Northeastern Brazil

Variables	**n**	**OR (95% CI)[1]**	***p-value***	**OR (95% CI)[2]**	***p-value***
Socio-Demographic / Behavioural Variables					
Gender					
Male	242	1.00 (reference)		1.00	
Female	472	2.65 (1.59-4.42)	< **0.001**	2.49 (1.24-5.00)	**0.010**
Age groups (years)					
20-35	235	1.00			

36-50	241	1.08 (0.65-1.79)	0.782		
≥ 51	238	1.31 (0.80-2.16)	0.284		
Ethnicity					
White	120	1.00			
Brown	576	1.50 (0.82-2.72)	0.188		
Black	18	0.95 (0.20-4.56)	0.945		
Education					
High School or Higher	206	1.00		1.00	
Primary School	413	1.21 (0.57-2.56)	0.619	1.12 (0.49-2.55)	0.796
Illiterate	95	1.92 (1.16-3.18)	**0.012**	1.52 (0.88-2.65)	0.137
Marital Status					
Single	159	1.00			
Married / Cohabitant	477	0.80 (0.49-1.30)	0.367		
Divorced / Separated	28	0.82 (0.26-2.54)	0.724		
Widow(er)	49	1.77 (0.83-3.77)	0.141		
Monthly Income					
≥ 2MW	71	1.00		1.00	
< 2MW	641	2.62 (1.03-6.65)	**0.043**	1.60 (0.59-4.29)	0.355
Occupation					
Manual Labor	67	1.00		1.00	
Not Manual Labor	647	3.12 (1.11-8.76)	**0.031**	1.99 (0.63-6.27)	0.239
Physical Activity					
High	56	1.00			
Moderate	184	1.20 (0.55-2.64)	0.650		
Low	474	0.90 (0.38-2.13)	0.811		
Smoking					
Never	428	1.00		1.00	
Previous	147	1.23 (0.73-2.09)	0.437	1.39 (0.79-2.48)	0.256
Current	139	1.99 (1.22-3.23)	**0.006**	1.93 (1.11-3.36)	**0.020**
Alcohol Consumption					
No	455	1.00		1.00	
≤ 4 times a month	243	0.61 (0.39-0.97)	**0.036**	0.84 (0.51-1.38)	0.485
> 4 times a month	16	1.08 (0.30-3.88)	0.904	1.19 (0.30-4.69)	0.808
Family History DM					
No	429	1.00			
Yes	285	1.23 (0.82-1.85)	0.323		
Family History Depression					
No	622	1.00		1.00	
Yes	92	2.84 (1.72-4.69)	< **0.001**	2.84 (1.67-4.82)	< **0.001**
Clinical Variables					
BMI (Kg/m^2)					
< 25	272	1.00			
25-29.99	266	0.82 (0.51-1.31)	0.396		
≥30	175	1.002 (0.60-1.67)	0.994		

Fasting Cortisol					
Low (<6.7)	31	1.00			
Normal (6.7 - 22.6)	630	0.62 (0.26-1.47)	0.275		
High (≥ 22.6)	48	0.49 (0.15-1.63)	0.244		
Fasting Insulin (micro UI/ml)	703	1.01 (0.98-1.05)	0.460		
Total Cholesterol (mmol/l)					
Desirable (< 5.2)	506	1.00			
Borderline High (5.2 - 6.2)	141	1.34 (0.83-2.18)	0.237		
High (≥ 6.2)	61	0.73 (0.32-1.67)	0.461		
Triglycerides (mmol/l)					
Desirable (< 1.7)	538	1.00			
Borderline High (1.7 - 2.3)	76	1.22 (0.64-2.32)	0.550		
High (≥ 2.3)	95	1.47 (0.85-2.57)	0.172		
HDL-C (mmol/l)	713	1.40 (0.26-7.40)	0.696		
LDL-C (mmol/l)					
Desirable (< 3.4)	512	1.00			
Borderline High (3.4 - 4.1)	97	1.27 (0.72-2.23)	0.411		
High (≥ 4.1)	70	0.82 (0.39-1.72)	0.601		
Body Fat Percentage	698	1.02 (1.00-1.05)	**0.046**	0.99 (0.96-1.02)	0.484
WHR					
Normal	221	1.00			
High	492	0.92 (0.60-1.43)	0.722		

HDRS: Hamilton Depression Rating Scale. OR: Odds Ratio. CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus. BMI: Body Mass Index. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. WHR: Waist-to-Hip Ratio.
1: Crude OR; 2: Adjusted OR for gender, education, monthly income, occupation, smoking, alcohol consumption, family history of depression and body fat percentage.

3.4 RELATIONSHIP BETWEEN DIABETES AND DEPRESSION (MADRS AND HDRS)

3.4.1 Characteristics of the Study Sample with or without Diabetes / Depression

When MADRS was applied to assess depression, it was found that 34 (4.8%) subjects had both diabetes and depression, 73 (10.2%) had depression but not diabetes, 80 (11.2%) diabetes without depression, and 526 (73.8%) were free from both the conditions. Those without both the diseases (diabetes and depression) had lower age, were more likely to be male and white, were more educated, were less likely to be widow (er), had a moderate / high level of physical activity and were more likely to drink alcohol. On the other hand, subjects

with both diabetes and depression were more likely to be older, women, brown, less educated, widow (er), and have a sedentary lifestyle. Those with diabetes but not depression had a middle / high income, were more likely to be married, have a sedentary lifestyle, previous smoker, and have a positive family history of diabetes, whereas subjects with only depression had low income, were more likely to be single or divorced / separated, current smoker and have a family history of depression (Table 3.21).

Table 3.21: Socio-Demographic and Behavioural Characteristics of 713 Subjects with or without Diabetes / Depression (MADRS ≥ 20)

Characteristics	**Healthy Subjects (Without Diabetes and Depression)**	**With Diabetes / Without Depression**	**With Depression / Without Diabetes**	**With Diabetes and Depression**
n = 713	526	80	73	34
	Mean or % (95% CI)	*Mean or % (95% CI)*	*Mean or % (95% CI)*	*Mean or % (95% CI)*
Age (years)	43.5 (42.1-44.8)	53.0 (49.6-56.4)	44.3 (40.7-47.9)	53.9 (48.5-59.2)
Gender				
Male	37.3% (33.2-41.5)	36.3% (26.3-47.5)	19.2% (11.6-30.1)	8.8% (2.7-25.2)
Female	62.7% (58.5-66.8)	63.7% (52.5-73.7)	80.8% (69.9-88.4)	91.2% (74.8-97.3)
Ethnicity				
White	17.8% (14.8-21.4)	15.0% (8.6-24.8)	15.1% (8.4-25.5)	8.8% (2.7-25.2)
Brown	79.3% (75.6-82.5)	85.0% (75.2-91.4)	82.2% (71.4-89.5)	88.3% (71.4-95.7)
Black	2.9% (1.7-4.7)	0%	2.7% (0.7-10.6)	2.9% (0.4-19.8)
Monthly Income				
Low (≤ 1MW)	60.7% (56.4-64.8)	57.5% (46.2-68.0)	75.3% (63.9-84.1)	73.5% (55.5-86.1)
Middle (1MW - 5MW)	38.5% (34.5-42.8)	41.2% (30.8-52.5)	24.7% (15.9-36.1)	26.5% (13.9-44.5)
High (≥ 5MW)	0.8% (0.3-2.0)	1.3% (0.2-8.7)	0%	0%
Education (years of study)	6.9 (6.5-7.3)	4.8 (3.9-5.8)	6.8 (5.8-7.8)	4.7 (3.6-5.9)
Marital Status				
Single	23.6% (20.2-27.5)	11.2% (5.9-20.5)	30.2% (20.5-41.9)	11.8% (4.3-28.6)
Married / Cohabitant	67.0% (62.9-70.9)	75.0% (64.1-83.4)	54.8% (43.1-66.0)	70.6% (52.5-83.9)
Divorced / Separated	4.2% (2.8-6.3)	1.3% (0.2-8.7)	6.8% (2.8-15.7)	0%
Widow(er)	5.2% (3.5-7.4)	12.5% (6.8-21.9)	8.2% (3.7-17.4)	17.6% (7.8-35.2)
Physical Activity				
Low	62.2% (57.9-66.2)	87.5% (78.1-93.2)	63.0% (51.2-73.5)	88.2% (71.4-95.7)
Moderate	28.7% (25.0-32.7)	12.5% (6.8-21.9)	28.8% (19.4-40.4)	5.9% (1.4-22.0)
High	9.1% (6.9-11.9)	0%	8.2% (3.7-17.4)	5.9% (1.4-22.0)
Smoking				
Never	63.3% (59.1-67.3)	55.0% (43.8-65.7)	45.2% (34.0-56.9)	52.9% (35.6-69.6)
Previous	19.2% (16.0-22.8)	27.5% (18.7-38.5)	21.9% (13.7-33.1)	20.6% (9.7-38.4)
Current	17.5% (14.5-21.0)	17.5% (10.5-27.7)	32.9% (22.9-44.7)	26.5% (13.9-44.5)

Alcohol Consumption (yes)	39.2% (35.1-43.4)	30.0% (20.8-41.1)	30.1% (20.5-41.9)	17.6% (7.8-35.2)
Family History DM (yes)	35.6% (31.6-39.8)	63.7% (52.5-73.7)	37.0% (26.5-48.8)	58.8% (41.0-74.6)
Family History Depression (yes)	11.0% (8.6-14.0)	8.8% (4.2-17.5)	26.0% (17.1-37.5)	23.5% (11.8-41.5)

MADRS: Montgomery-Åsberg Depression Rating Scale. CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus.

Following MADRS, healthy subjects had the lowest mean values of 2-hour plasma glucose, capillary HbA1c, fasting insulin, total cholesterol, LDL-C, body fat percentage, WHR (same as in those with only depression), and HDRS scores. On the other hand, those with both the conditions (diabetes and depression) had the highest mean values of FPG, 2-hour plasma glucose, capillary HbA1c, fasting insulin, total cholesterol, LDL-C, BMI and body fat percentage. The subjects with diabetes but not depression had the highest mean levels of fasting cortisol, triglycerides, WHR, SBP, and DBP, while those with only depression had the highest mean values of HDL-C, MADRS and HDRS scores (Table 3.22).

Table 3.22: Clinical Characteristics of 713 Subjects with or without Diabetes / Depression (MADRS ≥ 20)

Characteristics	**Healthy Subjects (Without Diabetes and Depression)**	**With Diabetes / Without Depression**	**With Depression / Without Diabetes**	**With Diabetes and Depression**
n = 713	526	80	73	34
	Mean (95% CI)	*Mean (95% CI)*	*Mean (95% CI)*	*Mean (95% CI)*
FPG (mmol/l)	4.75 (4.69-4.81)	9.35 (8.40-10.30)	4.64 (4.49-4.79)	9.40 (7.62-11.18)
2-hour Plasma Glucose (mmol/l)	6.36 (6.25-6.46)	15.56 (14.12-17.00)	6.46 (6.17-6.76)	15.98 (12.94-19.02)
Capillary HbA1c (%)	5.98 (5.93-6.02)	8.02 (7.57-8.48)	6.02 (5.89-6.15)	8.19 (7.32-9.07)
Fasting Cortisol (mcg/dl)	14.28 (13.84-14.71)	14.65 (13.41-15.88)	13.01 (11.94-14.08)	13.26 (11.43-15.08)
Fasting Insulin (micro UI/ml)	6.46 (6.08-6.84)	8.19 (6.44-9.94)	6.74 (5.74-7.73)	8.32 (6.31-10.32)
Total Cholesterol (mmol/l)	4.62 (4.54-4.71)	5.12 (4.90-5.34)	4.72 (4.51-4.92)	5.19 (4.80-5.57)
Triglycerides (mmol/l)	1.43 (1.28-1.58)	2.28 (1.78-2.78)	1.33 (1.11-1.56)	2.08 (1.65-2.51)
HDL-C (mmol/l)	1.23 (1.22-1.24)	1.21 (1.18-1.24)	1.24 (1.21-1.27)	1.19 (1.14-1.23)
LDL-C (mmol/l)	2.74 (2.65-2.83)	2.87 (2.62-3.12)	2.87 (2.68-3.06)	3.04 (2.70-3.39)
BMI (Kg/m^2)	26.49 (26.08-26.91)	29.08 (27.94-30.22)	25.57 (24.38-26.76)	30.28 (27.66-32.89)
Body Fat Percentage	31.81 (31.03-32.58)	36.07 (34.29-37.85)	34.07 (32.07-36.07)	37.95 (34.45-41.45)
WHR	0.90 (0.89-0.91)	0.99 (0.96-1.02)	0.90 (0.87-0.92)	0.97 (0.94-1.00)
SBP (mmHg)	126.2 (124.3-128.2)	139.9 (134.4-145.4)	120.4 (115.8-125.1)	136.3 (127.8-144.9)
DBP (mmHg)	76.21 (74.60-77.81)	82.40 (79.45-85.36)	73.92 (71.74-76.11)	78.04 (74.18-81.91)
MADRS score	5.57 (5.16-5.98)	4.96 (4.00-5.92)	24.75 (23.00-26.50)	23.24 (20.22-26.25)
HDRS score	4.54 (4.23-4.84)	5.24 (4.39-6.09)	17.68 (16.32-19.05)	17.35 (14.69-20.01)

MADRS: Montgomery-Åsberg Depression Rating Scale. CI: Confidence Interval. FPG: Fasting Plasma Glucose. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. BMI: Body Mass Index. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. HDRS: Hamilton Depression Rating Scale.

When HDRS was the tool used to evaluate depressive symptoms, it was observed that 35 (4.9%) subjects had both diabetes and depression, 76 (10.6%) had depression but not diabetes, 79 (11.1%) diabetes without depression, and 524 (73.4%) were free from both the conditions. Disease-free subjects were more likely to be male, white or black, had a higher level of education, were less likely to be widow (er), had a moderate / high level of physical activity and were more likely to drink alcohol. On the contrary, subjects with both diabetes and depression were more likely to be women, brown, widow (er), have a low level of physical activity, and low income. Those with diabetes but not depression were older, had a middle / high income, were more likely to be less educated, married, have a sedentary lifestyle, be previous smoker, and have a positive family history of diabetes, whereas subjects with only depression were younger, had a low income, were more likely to be single or divorced / separated, current smoker and have a family history of depression (Table 3.23).

Table 3.23: Socio-Demographic and Behavioural Characteristics of 714 Subjects with or without Diabetes / Depression (HDRS ≥ 14)

Characteristics	**Healthy Subjects (Without Diabetes and Depression)**	**With Diabetes / Without Depression**	**With Depression / Without Diabetes**	**With Diabetes and Depression**
n = 714	524	79	76	35
	Mean or % (95% CI)	*Mean or % (95% CI)*	*Mean or % (95% CI)*	*Mean or % (95% CI)*
Age (years)	43.6 (42.3-45.0)	53.8 (50.3-57.2)	43.3 (39.8-46.8)	52.2 (46.8-57.5)
Gender				
Male	37.2% (33.2-41.5)	34.2% (24.4-45.5)	19.7% (12.1-30.5)	14.3% (5.8-31.1)
Female	62.8% (58.5-66.8)	65.8% (54.5-75.6)	80.3% (69.5-87.9)	85.7% (68.9-94.2)
Ethnicity				
White	17.9% (14.9-21.5)	15.2% (8.7-25.1)	14.5% (8.1-24.6)	8.6% (2.6-24.6)
Brown	79.2% (75.5-82.5)	83.5% (73.4-90.3)	82.9% (72.5-89.9)	91.4% (75.4-97.4)
Black	2.9% (1.7-4.7)	1.3% (0.2-8.8)	2.6% (0.6-10.2)	0%
Monthly Income				
Low (≤ 1MW)	60.5% (56.3-64.7)	57.0% (45.6-67.6)	76.3% (65.2-84.7)	74.3% (56.5-86.5)
Middle (1MW - 5MW)	38.7% (34.6-43.0)	41.7% (31.2-53.1)	23.7% (15.3-34.8)	25.7% (13.5-43.5)
High (≥ 5MW)	0.8% (0.3-2.0)	1.3% (0.2-8.8)	0%	0%
Education (years of study)	6.9 (6.5-7.3)	4.8 (3.8-5.7)	6.7 (5.8-7.7)	4.9 (3.7-6.0)
Marital Status				
Single	23.5% (20.1-27.4)	11.3% (5.9-20.7)	30.3% (20.8-41.7)	11.4% (4.1-27.8)
Married / Cohabitant	67.1% (63.0-71.0)	74.7% (63.7-83.2)	55.2% (43.7-66.2)	71.4% (53.6-84.4)

Divorced / Separated	4.4% (2.9-6.5)	1.3% (0.2-8.8)	5.3% (1.9-13.5)	0%
Widow(er)	5.0% (3.4-7.2)	12.7% (6.9-22.2)	9.2% (4.4-18.4)	17.2% (7.6-34.3)
Physical Activity				
Low	62.2% (58.0-66.3)	87.3% (77.8-93.1)	63.2% (51.6-73.4)	88.6% (72.2-95.9)
Moderate	28.6% (24.9-32.7)	12.7% (6.9-22.2)	28.9% (19.7-40.4)	5.7% (1.3-21.4)
High	9.2% (7.0-12.0)	0%	7.9% (3.5-16.7)	5.7% (1.3-21.4)
Smoking				
Never	62.8% (58.5-66.8)	54.4% (43.2-65.3)	48.7% (37.5-60.1)	54.3% (37.1-70.5)
Previous	19.5% (16.3-23.1)	27.8% (18.9-39.0)	21.1% (13.2-31.9)	20.0% (9.5-37.4)
Current	17.7% (14.7-21.3)	17.8% (10.7-28.0)	30.2% (20.8-41.7)	25.7% (13.5-43.5)
Alcohol Consumption (yes)	39.5% (35.4-43.8)	26.6% (17.9-37.6)	28.9% (19.7-40.4)	25.7% (13.5-43.5)
Family History DM (yes)	35.3% (31.3-39.5)	64.6% (53.2-74.5)	38.2% (27.8-49.8)	57.1% (39.7-72.9)
Family History Depression (yes)	10.9% (8.5-13.9)	8.9% (4.2-17.7)	26.3% (17.5-37.6)	22.9% (11.4-40.5)

HDRS: Hamilton Depression Rating Scale. CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus.

Regarding clinical characteristics, disease-free subjects had the lowest mean values of 2-hour plasma glucose, fasting insulin, total cholesterol, LDL-C, body fat percentage, and HDRS scores. On the other hand, those with both the conditions (diabetes and depression) had the highest mean values of fasting insulin, total cholesterol, LDL-C, BMI and body fat percentage. The subjects with diabetes but not depression had the highest mean levels of FPG, 2-hour plasma glucose, capillary HbA1c, fasting cortisol, triglycerides, WHR, SBP, and DBP, while those with only depression had the highest mean values of HDL-C, MADRS and HDRS scores (Table 3.24).

Table 3.24: Clinical Characteristics of 714 Subjects with or without Diabetes / Depression (HDRS ≥ 14)

Characteristics	**Healthy Subjects (Without Diabetes and Depression)**	**With Diabetes / Without Depression**	**With Depression / Without Diabetes**	**With Diabetes and Depression**
n = 714	524	79	76	35
	Mean (95% CI)	*Mean (95% CI)*	*Mean (95% CI)*	*Mean (95% CI)*
FPG (mmol/l)	4.76 (4.70-4.81)	9.58 (8.55-10.60)	4.63 (4.49-4.78)	8.89 (7.38-10.41)
2-hour Plasma Glucose (mmol/l)	6.36 (6.25-6.46)	16.06 (14.54-17.58)	6.44 (6.16-6.73)	14.84 (12.10-17.59)
Capillary HbA1c (%)	5.99 (5.94-6.03)	8.10 (7.64-8.56)	5.98 (5.85-6.12)	8.01 (7.15-8.87)
Fasting Cortisol (mcg/dl)	14.26 (13.83-14.70)	14.53 (13.30-15.76)	13.18 (12.05-14.31)	13.58 (11.71-15.45)
Fasting Insulin (micro UI/ml)	6.49 (6.10-6.87)	8.20 (6.43-9.96)	6.55 (5.60-7.50)	8.31 (6.32-10.29)
Total Cholesterol (mmol/l)	4.62 (4.54-4.71)	5.10 (4.88-5.31)	4.68 (4.49-4.88)	5.23 (4.85-5.62)
Triglycerides (mmol/l)	1.43 (1.28-1.58)	2.23 (1.74-2.72)	1.33 (1.11-1.55)	2.20 (1.66-2.73)

HDL-C (mmol/l)	1.23 (1.22-1.24)	1.21 (1.18-1.23)	1.24 (1.21-1.27)	1.20 (1.15-1.24)
LDL-C (mmol/l)	2.74 (2.65-2.84)	2.87 (2.63-3.11)	2.84 (2.65-3.02)	3.03 (2.65-3.41)
BMI (Kg/m^2)	26.52 (26.10-26.94)	29.38 (28.23-30.53)	25.41 (24.30-26.52)	29.53 (27.00-32.06)
Body Fat Percentage	31.90 (31.12-32-67)	36.59 (34.79-38.39)	33.36 (31.41-35.32)	36.66 (33.25-40.07)
WHR	0.90 (0.89-0.91)	0.99 (0.96-1.02)	0.89 (0.87-0.92)	0.96 (0.94-0.99)
SBP (mmHg)	126.5 (124.6-128.5)	140.1 (134.6-145.7)	118.7 (114.4-122.9)	135.8 (127.4-144.3)
DBP (mmHg)	76.33 (74.72-77.94)	82.13 (79.22-85.03)	73.44 (71.30-75.60)	78.79 (74.60-82.98)
MADRS score	5.55 (5.14-5.97)	5.54 (4.27-6.82)	24.08 (22.27-25.88)	21.40 (18.03-24.77)
HDRS score	4.41 (4.13-4.70)	4.89 (4.18-5.60)	18.01 (16.77-19.26)	17.80 (15.35-20.25)

HDRS: Hamilton Depression Rating Scale. CI: Confidence Interval. FPG: Fasting Plasma Glucose. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. BMI: Body Mass Index. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. MADRS: Montgomery-Åsberg Depression Rating Scale.

3.4.2 Prevalence of DM among Depressed Subjects and Prevalence of Depression among Diabetics Compared to Disease-Free Individuals

When MADRS was used to assess depression, the prevalence of DM among those with depression (MADRS ≥ 20) was significantly higher compared to those without depression only among women (22.0% vs. 7.6%, p=0.001) (Figure 3.4). However, when HDRS was the tool used, the prevalence of DM among the subjects with depression (HDRS ≥ 14) was significantly higher compared to those without depression in both genders (Female: 22.6% vs. 7.4%, p<0.001 / Male: 25.0% vs. 6.9%, p=0.032) (Figure 3.5).

Figure 3.4: Prevalence of DM among Those with and without Depression (MADRS ≥ 20), by Gender

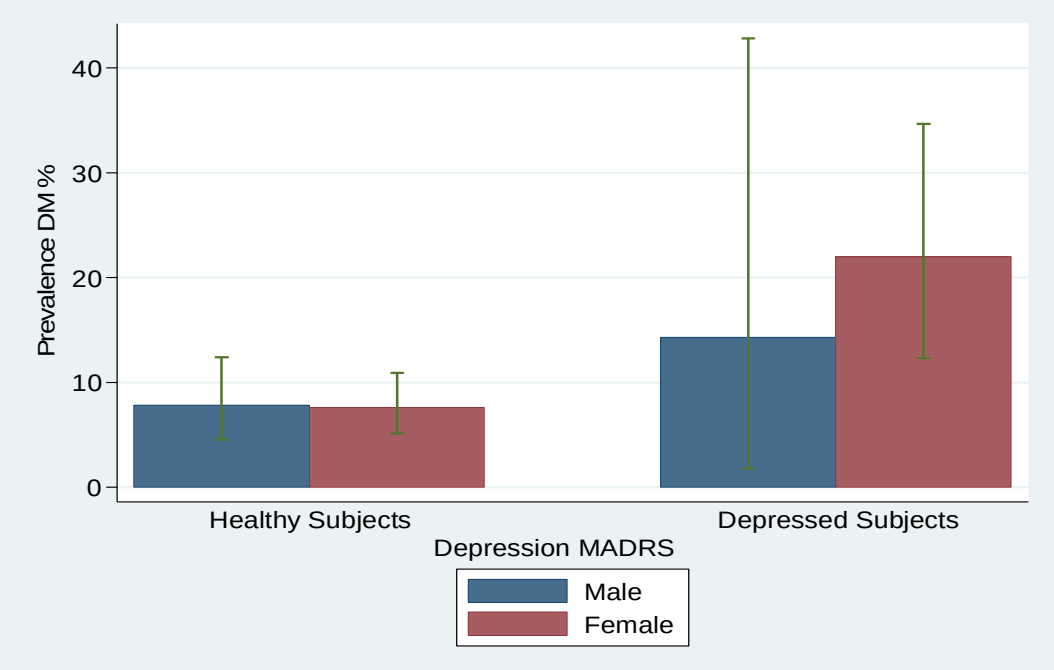
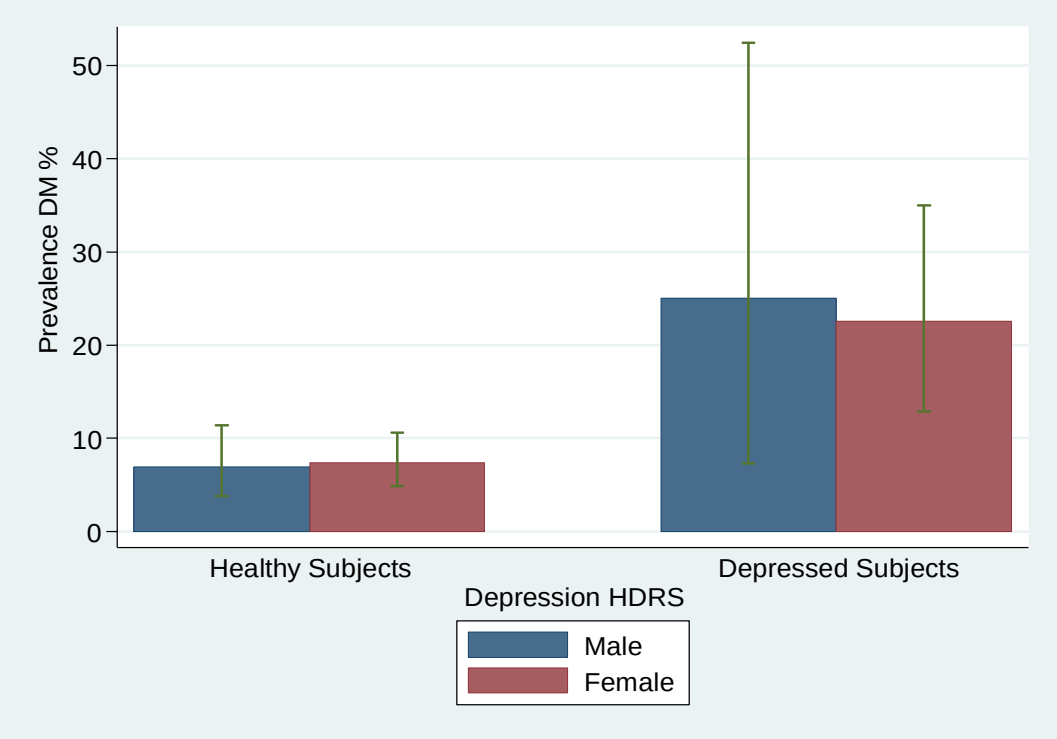


Figure 3.5: Prevalence of DM among Those with and without Depression (HDRS ≥ 14), by Gender



Similarly, when using MADRS, the prevalence of depression (MADRS ≥ 20) was significantly higher among diabetics compared to those without diabetes only among women (32.5% vs. 12.3%, p=0.001) (Figure 3.6). However, when HDRS was employed as a tool for assessing depression, the prevalence of depression (HDRS ≥ 14) was significantly higher among those with diabetes compared to those without diabetes for both genders (Female: 35.0% vs. 12.8%, p<0.001 / Male: 22.2% vs. 6.0%, p=0.032) (Figure 3.7).

Figure 3.6: Prevalence of Depression (MADRS ≥ 20) among Those with and without DM, by Gender

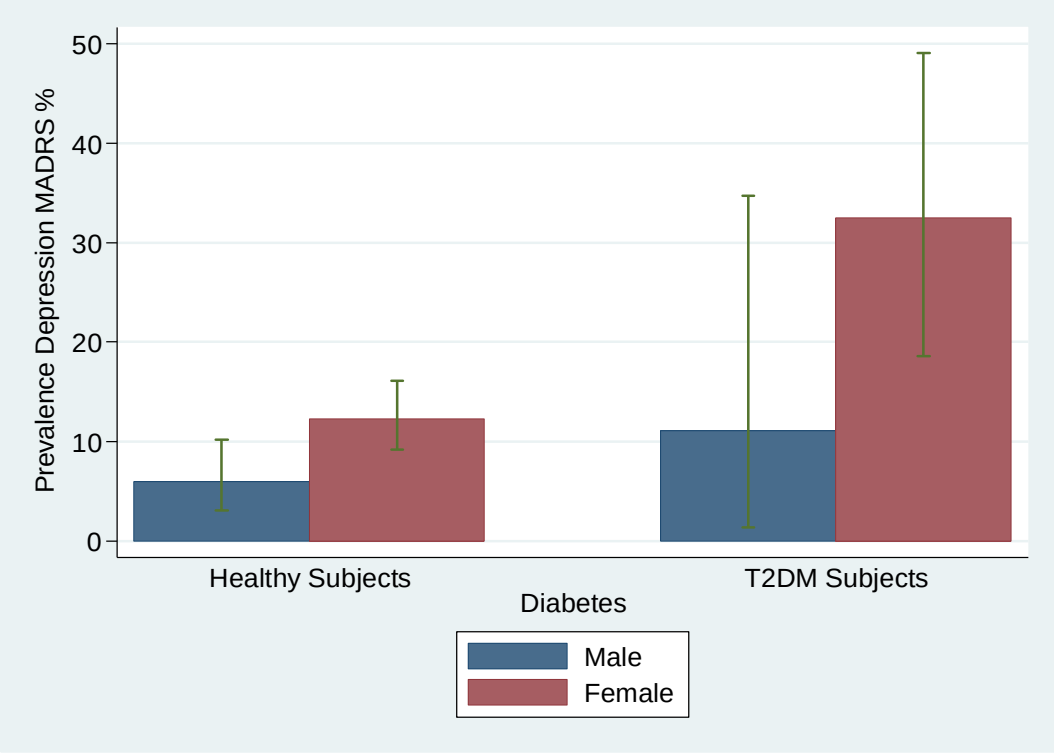
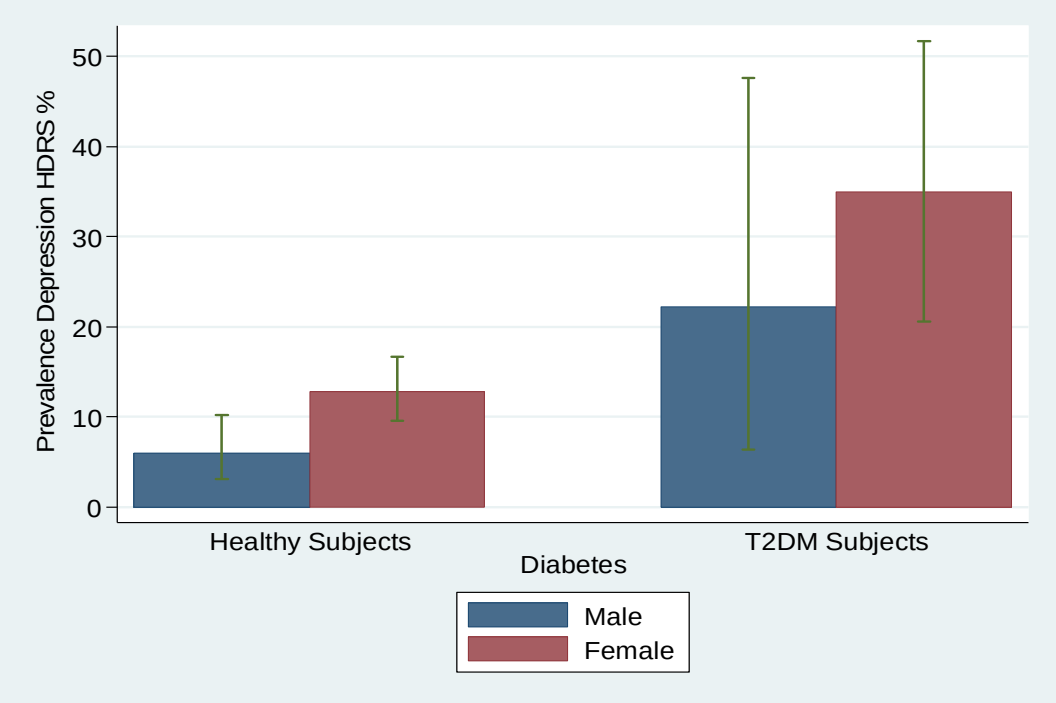


Figure 3.7: Prevalence of Depression (HDRS ≥ 14) among Those with and without DM, by Gender



3.4.3 Univariate and Multivariate Regression Models

When MADRS was applied to assess depression, the significant risk indicators for the occurrence of diabetes in univariate analysis were age, education, physical activity, family history of diabetes, depression (MADRS ≥ 20), BMI status, fasting insulin, total cholesterol, triglycerides, LDL-C, body fat percentage, WHR, SBP and DBP. Then, only these significant indicators in univariate analysis were further included in the multivariate regression model. Family history of DM, depression, triglycerides, body fat percentage, and WHR remained significant in multivariate analysis. The risk for developing diabetes was about 8 times higher among those with a high WHR and almost 4 times higher among depressed subjects (Table 3.25).

Table 3.25: Univariate and Multivariate Regression Models for the Relationship between Diabetes and Selected Socio-Demographic / Behavioural and Clinical Variables (Including Depression - MADRS ≥ 20) in 632 Subjects from Northeastern Brazil

Variables	n	OR (95% CI)[1]	*p-value*	OR (95% CI)[2]	*p-value*
Socio-Demographic / Behavioural Variables					
Gender					
Male	218	1.00 (reference)			
Female	414	1.19 (0.66-2.13)	0.561		
Age groups (years)					
20-35	229	1.00		1.00	
36-50	214	2.07 (0.99-4.30)	**0.050**	0.79 (0.32-1.99)	0.623
≥ 51	189	2.63 (1.28-5.41)	**0.009**	0.45 (0.16-1.27)	0.132
Ethnicity					
White	108	1.00			
Brown	507	1.34 (0.61-2.91)	0.464		
Black	17	0.78 (0.09-6.67)	0.822		
Education					
High School or Higher	199	1.00		1.00	
Primary School	353	3.02 (1.18-7.73)	**0.022**	3.22 (0.84-12.25)	0.087
Illiterate	80	2.62 (1.24-5.53)	**0.011**	2.02 (0.77-5.33)	0.156
Monthly Income					
< 2MW	569	1.00			
≥ 2MW	61	1.84 (0.86-3.95)	0.120		
Occupation					
Manual Labor	65	1.00			
Not Manual Labor	567	2.22 (0.67-7.32)	0.190		

Physical Activity					
High	53	1.00		1.00	
Moderate	167	7.51 (1.02-55.50)	**0.048**	2.71 (0.30-24.59)	0.375
Low	412	1.61 (0.18-14.05)	0.669	0.78 (0.08-8.22)	0.839
Smoking					
Never	387	1.00			
Previous	126	1.49 (0.78-2.87)	0.222		
Current	119	1.13 (0.55-2.32)	0.739		
Alcohol Consumption					
No	388	1.00			
≤ 4 times a month	229	1.07 (0.61-1.88)	0.808		
> 4 times a month	15	0.72 (0.09-5.64)	0.755		
Family History DM					
No	394	1.00		1.00	
Yes	238	2.57 (1.48-4.45)	**0.001**	3.08 (1.56-6.06)	**0.001**
Family History Depression					
No	553	1.00			
Yes	79	0.96 (0.42-2.19)	0.917		
Clinical Variables					
Depression (MADRS ≥ 20)					
No	558	1.00		1.00	
Yes	73	3.10 (1.62-5.92)	**0.001**	3.90 (1.69-8.99)	**0.001**
BMI Status					
< 25	243	1.00		1.00	
25-29.99	237	2.66 (1.20-5.91)	**0.016**	0.75 (0.27-2.07)	0.580
≥30	152	5.62 (2.56-12.31)	< **0.001**	1.18 (0.35-3.98)	0.785
Fasting Cortisol (mcg/dl)					
Low (<6.7)	27	1.00			
Normal (6.7 - 22.6)	556	1.21 (0.28-5.25)	0.801		
High (≥ 22.6)	45	2.30 (0.44-12.00)	0.322		
Fasting Insulin (micro UI/ml)	622	1.08 (1.03-1.14)	**0.001**	0.99 (0.91-1.06)	0.686
Total Cholesterol (mmol/l)					
Desirable (< 5.2)	452	1.00		1.00	
Borderline High (5.2 - 6.2)	123	2.57 (1.39-4.75)	**0.003**	1.79 (0.61-5.22)	0.287
High (≥ 6.2)	52	2.56 (1.11-5.92)	**0.028**	3.03 (0.38-24.37)	0.298
Triglycerides (mmol/l)					
Desirable (< 1.7)	483	1.00		1.00	
Borderline High (1.7 - 2.3)	68	3.36 (1.62-6.95)	**0.001**	2.44 (1.03-5.80)	**0.044**
High (≥ 2.3)	77	4.44 (2.30-8.55)	< **0.001**	2.95 (1.11-7.84)	**0.030**
HDL-C (mmol/l)	631	1.10 (0.12-10.24)	0.936		
LDL-C (mmol/l)					
Desirable (< 3.4)	456	1.00		1.00	

Borderline High (3.4 - 4.1)	86	2.54 (1.32-4.89)	**0.005**	1.61 (0.53-4.90)	0.399
High (≥ 4.1)	62	1.06 (0.40-2.80)	0.914	0.24 (0.03-1.84)	0.167
Body Fat Percentage	622	1.08 (1.04-1.12)	< **0.001**	1.06 (1.004-1.11)	**0.034**
WHR					
Normal	211	1.00		1.00	
High	421	16.03 (3.87-66.37)	< **0.001**	8.11 (1.73-38.00)	**0.008**
SBP (mmHg)					
< 140	483	1.00		1.00	
≥ 140	147	2.79 (1.60-4.88)	< **0.001**	1.91 (0.75-4.89)	0.175
DBP (mmHg)					
< 90	563	1.00		1.00	
≥ 90	67	4.33 (2.29-8.17)	< **0.001**	1.98 (0.77-5.10)	0.159

MADRS: Montgomery-Åsberg Depression Rating Scale. OR: Odds Ratio. CI: Confidence Interval. MW: Brazilian Minimum Wage in 2012. DM: Diabetes Mellitus. BMI: Body Mass Index. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure.
1: Crude OR; 2: Adjusted OR for age, education, physical activity, family history of diabetes, depression (MADRS ≥ 20), BMI status, fasting insulin, total cholesterol, triglycerides, LDL-C, body fat percentage, WHR, SBP and DBP.
MADRS and HDL-C have 1 missing value; monthly income, SBP and DBP have 2 missing values; fasting cortisol and triglycerides have 4; total cholesterol has 5; fasting insulin and body fat percentage have 10; and LDL-C has 28.

In the same way, when HDRS was used, age, education, physical activity, family history of diabetes, depression (HDRS ≥ 14), BMI status, fasting insulin, total cholesterol, triglycerides, LDL-C, body fat percentage, WHR, SBP and DBP were found to be significant indicators of diabetes in univariate analysis. Again, family history of DM, depression, triglycerides, body fat percentage, and WHR remained significant in multivariate analysis, controlling for age, education, physical activity, family history of diabetes, depression (HDRS ≥ 14), BMI status, fasting insulin, total cholesterol, triglycerides, LDL-C, body fat percentage, WHR, SBP and DBP. The risk for developing diabetes was more than 8 times higher among those with a high WHR and more than 4 times higher among those classified as depressed (Table 3.26).

Table 3.26: Univariate and Multivariate Regression Models for the Relationship between Diabetes and Selected Socio-Demographic / Behavioural and Clinical Variables (Including Depression - HDRS ≥ 14) in 632 Subjects from Northeastern Brazil

Variables	n	OR (95% CI)[1]	*p-value*	OR (95% CI)[2]	*p-value*
Socio-Demographic / Behavioural Variables					
Gender					
Male	218	1.00 (reference)			
Female	414	1.19 (0.66-2.13)	0.561		
Age groups (years)					
20-35	229	1.00		1.00	
36-50	214	2.07 (0.99-4.30)	**0.050**	0.83 (0.33-2.10)	0.692
≥ 51	189	2.63 (1.28-5.41)	**0.009**	0.45 (0.16-1.28)	0.134
Ethnicity					
White	108	1.00			
Brown	507	1.34 (0.61-2.91)	0.464		
Black	17	0.78 (0.09-6.67)	0.822		
Education					
High School or Higher	199	1.00		1.00	
Primary School	353	3.02 (1.18-7.73)	**0.022**	3.09 (0.81-11.76)	0.099
Illiterate	80	2.62 (1.24-5.53)	**0.011**	1.89 (0.71-5.03)	0.205
Monthly Income					
< 2MW	569	1.00			
≥ 2MW	61	1.84 (0.86-3.95)	0.120		
Occupation					
Manual Labor	65	1.00			
Not Manual Labor	567	2.22 (0.67-7.32)	0.190		
Physical Activity					
High	53	1.00		1.00	
Moderate	167	7.51 (1.02-55.50)	**0.048**	2.53 (0.28-23.15)	0.412
Low	412	1.61 (0.18-14.05)	0.669	0.75 (0.07-7.91)	0.808
Smoking					
Never	387	1.00			
Previous	126	1.49 (0.78-2.87)	0.222		
Current	119	1.13 (0.55-2.32)	0.739		
Alcohol Consumption					
No	388	1.00			
≤ 4 times a month	229	1.07 (0.61-1.88)	0.808		
> 4 times a month	15	0.72 (0.09-5.64)	0.755		
Family History DM					
No	394	1.00		1.00	
Yes	238	2.57 (1.48-4.45)	**0.001**	3.03 (1.54-5.98)	**0.001**
Family History Depression					

No	553	1.00			
Yes	79	0.96 (0.42-2.19)	0.917		
Clinical Variables					
Depression (HDRS ≥ 14)					
No	554	1.00		1.00	
Yes	78	3.86 (2.08-7.15)	< **0.001**	4.55 (2.02-10.29)	< **0.001**
BMI Status					
< 25	243	1.00		1.00	
25-29.99	237	2.66 (1.20-5.91)	**0.016**	0.78 (0.28-2.16)	0.632
≥30	152	5.62 (2.56-12.31)	< **0.001**	1.14 (0.34-3.86)	0.832
Fasting Cortisol (mcg/dl)					
Low (<6.7)	27	1.00			
Normal (6.7 - 22.6)	556	1.21 (0.28-5.25)	0.801		
High (≥ 22.6)	45	2.30 (0.44-12.00)	0.322		
Fasting Insulin (micro UI/ml)	622	1.08 (1.03-1.14)	**0.001**	0.98 (0.91-1.06)	0.678
Total Cholesterol (mmol/l)					
Desirable (< 5.2)	452	1.00		1.00	
Borderline High (5.2 - 6.2)	123	2.57 (1.39-4.75)	**0.003**	1.76 (0.61-5.08)	0.297
High (≥ 6.2)	52	2.56 (1.11-5.92)	**0.028**	2.68 (0.33-21.78)	0.355
Triglycerides (mmol/l)					
Desirable (< 1.7)	483	1.00		1.00	
Borderline High (1.7 - 2.3)	68	3.36 (1.62-6.95)	**0.001**	2.52 (1.06-6.01)	**0.037**
High (≥ 2.3)	77	4.44 (2.30-8.55)	< **0.001**	3.04 (1.15-8.05)	**0.025**
HDL-C (mmol/l)	631	1.10 (0.12-10.24)	0.936		
LDL-C (mmol/l)					
Desirable (< 3.4)	456	1.00		1.00	
Borderline High (3.4 - 4.1)	86	2.54 (1.32-4.89)	**0.005**	1.68 (0.55-5.07)	0.362
High (≥ 4.1)	62	1.06 (0.40-2.80)	0.914	0.26 (0.03-1.98)	0.193
Body Fat Percentage	622	1.08 (1.04-1.12)	< **0.001**	1.06 (1.01-1.12)	**0.016**
WHR					
Normal	211	1.00		1.00	
High	421	16.03 (3.87-66.37)	< **0.001**	8.40 (1.78-39.55)	**0.007**
SBP (mmHg)					
< 140	483	1.00		1.00	
≥ 140	147	2.79 (1.60-4.88)	< **0.001**	2.15 (0.84-5.51)	0.110
DBP (mmHg)					
< 90	563	1.00		1.00	
≥ 90	67	4.33 (2.29-8.17)	< **0.001**	1.88 (0.73-4.84)	0.190

HDRS: Hamilton Depression Rating Scale. OR: Odds Ratio. CI: Confidence Interval. MW: Brazilian Minimum Wage in 2012. DM: Diabetes Mellitus. BMI: Body Mass Index. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. WHR: Waist-to-Hip Ratio. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure.

1: Crude OR; 2: Adjusted OR for age, education, physical activity, family history of diabetes, depression (HDRS ≥ 14), BMI status, fasting insulin, total cholesterol, triglycerides, LDL-C, body fat percentage, WHR, SBP and DBP.

In univariate analysis, the significant risk indicators for the occurrence of depression (MADRS ≥ 20) were gender, smoking, family history of depression, diabetes, triglycerides and body fat percentage. However, in multivariate analysis, only gender, smoking, diabetes and family history of depression remained significant after adjusting for gender, smoking, family history of depression, diabetes, triglycerides and body fat percentage. The risk for developing depression was approximately 3 times higher among women and individuals with diabetes (Table 3.27).

Table 3.27: Univariate and Multivariate Regression Models for the Relationship between Depression (MADRS ≥ 20) and Selected Socio-Demographic / Behavioural and Clinical Variables (Including Diabetes) in 631 Subjects from Northeastern Brazil

Variables	**n**	**OR (95% CI)[1]**	***p-value***	**OR (95% CI)[2]**	***p-value***
Socio-Demographic / Behavioural Variables					
Gender					
Male	218	1.00 (reference)		1.00	
Female	413	2.43 (1.32-4.46)	**0.004**	3.20 (1.46-7.00)	**0.004**
Age groups (years)					
20-35	228	1.00			
36-50	214	0.89 (0.49-1.62)	0.705		
≥ 51	189	1.18 (0.66-2.13)	0.572		
Ethnicity					
White	108	1.00			
Brown	506	1.34 (0.67-2.72)	0.411		
Black	17	1.31 (0.26-6.55)	0.745		
Education					
High School or Higher	199	1.00			
Primary School	352	1.20 (0.52-2.78)	0.669		
Illiterate	80	1.39 (0.79-2.45)	0.256		
Marital Status					
Single	151	1.00			
Married / Cohabitant	418	0.67 (0.38-1.18)	0.168		
Divorced / Separated	25	0.84 (0.23-3.07)	0.797		

Widow(er)	36	1.77 (0.71-4.40)	0.220		
Monthly Income					
≥ 2MW	61	1.00			
< 2MW	568	2.72 (0.83-8.91)	0.099		
Occupation					
Manual Labor	65	1.00			
Not Manual Labor	566	2.92 (0.89-9.54)	0.077		
Physical Activity					
High	53	1.00			
Moderate	167	0.89 (0.38-2.10)	0.787		
Low	411	0.75 (0.29-1.91)	0.539		
Smoking					
Never	387	1.00		1.00	
Previous	125	1.52 (0.81-2.87)	0.191	1.77 (0.90-3.47)	0.097
Current	119	2.49 (1.40-4.42)	**0.002**	2.67 (1.45-4.93)	**0.002**
Alcohol Consumption					
No	388	1.00			
≤ 4 times a month	228	0.69 (0.40-1.18)	0.170		
> 4 times a month	15	1.04 (0.23-4.75)	0.960		
Family History DM					
No	393	1.00			
Yes	238	1.10 (0.67-1.81)	0.707		
Family History Depression					
No	552	1.00		1.00	
Yes	79	2.67 (1.47-4.83)	**0.001**	2.51 (1.32-4.76)	**0.005**
Clinical Variables					
Diabetes					
No	573	1.00		1.00	
Yes	58	3.10 (1.62-5.92)	**0.001**	3.00 (1.45-6.21)	**0.003**
BMI (Kg/m^2)					
< 25	243	1.00			
25-29.99	236	0.70 (0.39-1.25)	0.233		
≥30	152	1.04 (0.57-1.89)	0.908		
Fasting Cortisol					
Low (<6.7)	27	1.00			
Normal (6.7 - 22.6)	555	0.57 (0.21-1.57)	0.278		
High (≥ 22.6)	45	0.31 (0.07-1.44)	0.136		
Fasting Insulin (micro UI/ml)	621	1.04 (0.99-1.09)	0.114		
Total Cholesterol (mmol/l)					
Desirable (< 5.2)	451	1.00			
Borderline High (5.2 - 6.2)	123	1.38 (0.77-2.46)	0.282		
High (≥ 6.2)	52	0.67 (0.23-1.93)	0.457		

Triglycerides (mmol/l)					
Desirable (< 1.7)	482	1.00		1.00	
Borderline High (1.7 - 2.3)	68	1.56 (0.75-3.25)	0.236	1.23 (0.57-2.68)	0.598
High (≥ 2.3)	77	2.01 (1.05-3.85)	**0.036**	1.57 (0.77-3.23)	0.219
HDL-C (mmol/l)	630	1.98 (0.26-15.05)	0.510		
LDL-C (mmol/l)					
Desirable (< 3.4)	455	1.00			
Borderline High (3.4 - 4.1)	86	1.02 (0.50-2.10)	0.958		
High (≥ 4.1)	62	0.99 (0.43-2.28)	0.974		
Body Fat Percentage	621	1.03 (1.001-1.06)	**0.039**	0.99 (0.96-1.03)	0.633
WHR					
Normal	211	1.00			
High	420	1.03 (0.61-1.73)	0.914		

MADRS: Montgomery-Åsberg Depression Rating Scale. OR: Odds Ratio. CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus. BMI: Body Mass Index. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. WHR: Waist-to-Hip Ratio.
1: Crude OR; 2: Adjusted OR for gender, smoking habits, family history of depression, diabetes, triglycerides and body fat percentage.
Marital status and HDL-C have 1 missing value; monthly income has 2 missing values; triglycerides and fasting cortisol have 4; total cholesterol has 5; fasting insulin and body fat percentage have 10; and LDL-C has 28.

Following HDRS, the significant risk indicators for the occurrence of depression in univariate analysis were gender, education level, occupation, smoking, family history of depression, diabetes and triglycerides. In multivariate analysis, gender, smoking, diabetes and family history of depression remained significant after adjustment for the potential confounding factors (Table 3.28).

Table 3.28: Univariate and Multivariate Regression Models for the Relationship between Depression (HDRS ≥ 14) and Selected Socio-Demographic / Behavioural and Clinical Variables (including Diabetes) in 632 Subjects from Northeastern Brazil

Variables	**n**	**OR (95% CI)[1]**	***p-value***	**OR (95% CI)[2]**	***p-value***
Socio-Demographic / Behavioural Variables					
Gender					
Male	218	1.00 (reference)		1.00	
Female	414	2.22 (1.25-3.96)	**0.007**	2.17 (1.12-4.23)	**0.023**
Age groups (years)					
20-35	229	1.00			

36-50	214	0.99 (0.56-1.76)	0.980		
≥ 51	189	1.04 (0.58-1.87)	0.884		
Ethnicity					
White	108	1.00			
Brown	507	1.49 (0.74-3.00)	0.262		
Black	17	0.61 (0.07-5.12)	0.651		
Education					
High School or Higher	199	1.00		1.00	
Primary School	353	1.12 (0.47-2.68)	0.804	0.94 (0.36-2.48)	0.905
Illiterate	80	1.74 (0.99-3.06)	**0.056**	1.34 (0.73-2.48)	0.345
Marital Status					
Single	151	1.00			
Married / Cohabitant	419	0.71 (0.41-1.22)	0.212		
Divorced / Separated	25	0.51 (0.11-2.32)	0.383		
Widow(er)	36	1.96 (0.81-4.71)	0.135		
Monthly Income					
≥ 2MW	61	1.00			
< 2MW	569	2.13 (0.75-6.04)	0.155		
Occupation					
Manual Labor	65	1.00		1.00	
Not Manual Labor	567	3.15 (0.96-10.29)	**0.057**	1.88 (0.51-6.99)	0.344
Physical Activity					
High	53	1.00			
Moderate	167	0.99 (0.43-2.31)	0.984		
Low	412	0.75 (0.29-1.91)	0.539		
Smoking					
Never	387	1.00		1.00	
Previous	126	1.39 (0.76-2.56)	0.287	1.50 (0.77-2.93)	0.240
Current	119	2.02 (1.15-3.58)	**0.015**	2.03 (1.09-3.81)	**0.027**
Alcohol Consumption					
No	388	1.00			
≤ 4 times a month	229	0.71 (0.42-1.19)	0.188		
> 4 times a month	15	0.97 (0.21-4.43)	0.971		
Family History DM					
No	394	1.00			
Yes	238	1.25 (0.77-2.02)	0.366		
Family History Depression					
No	553	1.00		1.00	
Yes	79	2.65 (1.48-4.75)	**0.001**	2.49 (1.33-4.66)	**0.004**
Clinical Variables					
Diabetes					
No	574	1.00		1.00	
Yes	58	3.86 (2.08-7.15)	**< 0.001**	3.51 (1.78-6.90)	**< 0.001**

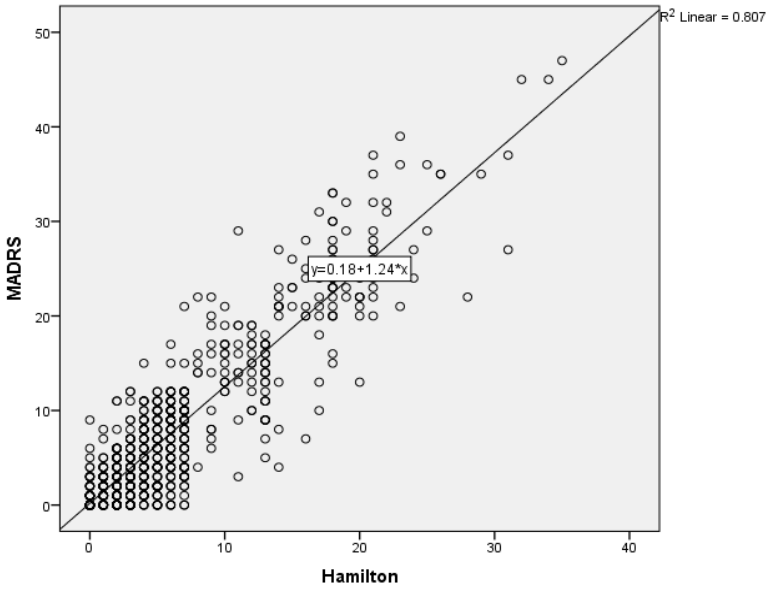
BMI (Kg/m^2)					
< 25	243	1.00			
25-29.99	237	0.72 (0.41-1.25)	0.244		
≥30	152	1.02 (0.57-1.84)	0.947		
Fasting Cortisol					
Low (<6.7)	27	1.00			
Normal (6.7 - 22.6)	556	0.60 (0.22-1.65)	0.323		
High (≥ 22.6)	45	0.55 (0.14-2.11)	0.383		
Fasting Insulin (micro UI/ml)	622	1.04 (0.99-1.09)	0.127		
Total Cholesterol (mmol/l)					
Desirable (< 5.2)	452	1.00			
Borderline High (5.2 - 6.2)	123	1.35 (0.77-2.37)	0.303		
High (≥ 6.2)	52	0.61 (0.21-1.77)	0.367		
Triglycerides (mmol/l)					
Desirable (< 1.7)	483	1.00		1.00	
Borderline High (1.7 - 2.3)	68	1.43 (0.69-2.97)	0.338	1.08 (0.50-2.36)	0.838
High (≥ 2.3)	77	2.01 (1.07-3.78)	**0.031**	1.42 (0.70-2.85)	0.330
HDL-C (mmol/l)	631	2.71 (0.37-19.64)	0.323		
LDL-C (mmol/l)					
Desirable (< 3.4)	456	1.00			
Borderline High (3.4 - 4.1)	86	1.18 (0.60-2.32)	0.625		
High (≥ 4.1)	62	0.78 (0.32-1.90)	0.586		
Body Fat Percentage	622	1.02 (0.99-1.05)	0.190		
WHR					
Normal	211	1.00			
High	421	0.94 (0.57-1.55)	0.806		

HDRS: Hamilton Depression Rating Scale. OR: Odds Ratio. CI: Confidence Interval. MW: Minimum Wage in 2012. DM: Diabetes Mellitus. BMI: Body Mass Index. HDL-C: High-Density Lipoprotein Cholesterol. LDL-C: Low-Density Lipoprotein Cholesterol. WHR: Waist-to-Hip Ratio.
1: Crude OR; 2: Adjusted OR for gender, education level, occupation, smoking, family history of depression, diabetes and triglycerides.

3.5 CORRELATION BETWEEN MADRS AND HDRS

The correlation between MADRS and HDRS scores was obtained with the Pearson's correlation coefficient. It was positive and significant ($r=0.91$, $p < 0.001$), as shown in Figure 3.8.

Figure 3.8: Correlation (r=0.91, p < 0.001) between the Total Scores of 714 Subjects Assessed by HDRS, and 713 by MADRS



Furthermore, when measuring the level of agreement between MADRS and HDRS, a Kappa of 0.913 was found (p < 0.001) (Table 3.29).

Table 3.29: Agreement between MADRS and HDRS

		Depression according to MADRS		
		No Depression	Depression	Total
Depression according to HDRS	No Depression	596	6	602
	Depression	10	101	111
	Total	606	107	713

MADRS: Montgomery-Åsberg Depression Rating Scale. HDRS: Hamilton Depression Rating Scale.

CHAPTER 4

DISCUSSION

4.1 METHODOLOGICAL DISCUSSION

4.1.1 Study Design

This research study was an observational inquiry and was based on a cross-sectional design. It was observational since no intervention (active attempt to make changes regarding the determinants or the progress of diseases) took place. It included a descriptive aspect, since the occurrence of diabetes and depression were investigated, as well as an analytical aspect, since it was investigated whether and to what extent both the conditions were associated (97).

Often called prevalence studies, cross-sectional studies allow the investigation of a disease prevalence and its risk indicators in relation to the socio-economic, demographic and health-related characteristics of the population under study. The major aim of cross-sectional studies is to describe individuals in the population and their simultaneous exposure at a particular point in time. Furthermore, they are relatively easy to carry out, can be completed rapidly (data are collected only at one point in time), usually are not very resource-intensive, and numerous variables can be analyzed at once (97). Another advantage of using such a design is the uncommon existence of major ethical difficulties, since the study participants are not deliberately exposed, treated, or not treated (98).

Considering the fact that in cross-sectional studies the measurements of the exposures and effects are carried out simultaneously, it is not easy to assess the causes for the associations found. Moreover, a cause-effect relationship or the sequence of the events cannot be determined. On the other hand, follow-up studies, also called cohort or incidence studies, can provide the best information about the potential causes to certain disease (the sequence of the events can be observed), and the most direct measurement of the risk of getting the disease (97). Therefore, such a design would be the most appropriate methodology to provide a better understanding of the directionality of the relationship between diabetes and depression, i.e. a cohort study would provide a clearer answer to this *"chicken-or-the-egg dilemma"* – which one comes first: diabetes or depression? (76). However, prospective cohort studies usually require the involvement of a large study population, are resource-intensive, and take a long time to be completed (97). Despite its limitations, a cross-sectional design was chosen due to the limited time frame and budget available, as well as because of the valuable and useful data that could be generated. Even though it limits the conclusions regarding the causal nature and the direction of the relationship, questions about the very existence of the association in northeastern Brazil could be assessed. As described previously,

data about the magnitude of depression in subjects with type 2 diabetes in Brazil are scarce. Thus in order to generate some epidemiological evidence regarding such an association in Brazilians, this cross-sectional study was conducted. Moreover, through the study, it was possible to find out the prevalence of the diseases, and establish some risk indicators. When investigating chronic diseases like diabetes, in which the cause of the disease has been somewhat established, data from cross-sectional surveys may also serve as a foundation for developing or strengthening hypotheses about related risk factors, as well as promoting the development of new management and preventive guidelines. It is also noteworthy to mention that although the study design applied here was similar to previous classical cross-sectional epidemiological studies, the participants were mostly newly diagnosed with diabetes and usually not aware of their blood glucose status.

4.1.2 Population and Sample Size

In this study, eight hundred and six subjects were randomly selected and invited to participate. Out of these, seven hundred and fourteen agreed to join the study (participation rate: 88.6%). Among 92 individuals who refused, 63% were males. The estimated sample size (approximately 530 subjects) required to have a statistical power of 90%, at a significance level of 0.05 was reached.

In the process of hypothesis testing, two types of error can occur. Type I error (α), also called an error of the first kind, involves the rejection of the null hypothesis when the null hypothesis is true, that is, when the data lead us to believe that there is a difference when in reality there is not. Type II error (β), also known as an error of the second kind, occurs when the null hypothesis is not rejected when in reality it is false, that is, when we conclude that there is not a difference but in reality there is (99). In this study, a proper sample size calculation was difficult to be made due to missing data on depression and diabetes in the population under investigation. Thus the possibility that type II errors occurred in the inferences made cannot be entirely ruled out. However, the sample size was reasonably large which could increase the precision.

4.1.3 Assessment of Depression

Although there is a large number of scales available for evaluating depressive conditions, the MADRS (91) and HDRS (92) are the two most common rating scales in use. They are not diagnostic instruments, but rather methods of comprehensively surveying the

type and magnitude of depressive symptoms. Moreover, they are usually applied to establish clinical criteria for distinguishing levels of illness severity and for measuring evolution of and recovery from a depressive episode (100).

Considered the “gold standard” of depression measures, the HDRS has served as a reference point for more recently developed scales. Since it was first introduced by Hamilton, many studies about the HDRS have been performed (101). A review of studies published between 1979 and 2003 has shown good internal, interrater, and retest reliability estimates for the overall scale, but weak interrater and retest coefficients at the item level (102). On the other hand, the MADRS items have been conceptualized to solve some of the psychometric limitations of the HDRS and to measure change during treatment. Of note, the MADRS does not focus on somatic symptoms as much as the HDRS does, therefore the interference of organic dysfunctions or treatment side effects can be minimized (101).

Although there is ample evidence indicating that both scales are valid measures of symptom outcome in major depression, reliability and validity studies in Brazil are rare (101). In a study from 1987 conducted in São Paulo, the MADRS was applied to a Brazilian depressed population, and its performance compared with those of the HDRS, the Visual Analogue Mood Scale (VAMS), and the global clinical assessment of independent Brazilian psychiatrists. A significant correlation was observed between MADRS and the three other assessments, indicating that the MADRS is a useful and operational instrument to evaluate depressed patients in Brazil. However, the results indicated that the HDRS had a lower sensitivity and specificity compared to MADRS (103). According to another study conducted in Brazil, it was observed that both MADRS and HDRS had good levels of reliability and validity, suggesting that they were able to measure the gravity of depressive symptoms (101).

4.1.4 Errors

Epidemiological studies aim to produce accurate measures of disease occurrence (or other outcomes). Although there are many possibilities for errors in measurements, researchers should attempt to minimize errors as much as possible and assess the impact of errors that cannot be eliminated. Sources of error can be systematic or random. A systematic error, also called bias, takes place when the results differ from the true values in a systematic way, towards one direction. On the other hand, random errors will not influence the results only in one direction (the effects of random errors can go either of the two ways). Random errors occur when a value of the sample measurement diverges from that of the true

population value due to chance alone. If the sample size is large enough, the effects of random errors will be balanced (97). Since the sample in this study was reasonably large, it is unlikely that random errors had a significant effect on the results.

4.1.4.1 Selection Bias

The systematic introduction of error may occur during the selection of the study participants and is known as selection bias. Selection bias takes place when there is a systematic difference between the characteristics of the people selected for a study and the characteristics of those who were not (97).

In this study, by using a probability sampling method, the selection bias / sampling errors could be minimized since all citizens in the health registry list of the city had equal chance to be selected. However, the list used to select the subjects had been updated for the last time only three years ago. Given the possible changes in the population that might have happened in this period (e.g., migration), as well as the potential mistakes that might have occurred when making the list (some individuals might have been left out); the possibility of some degree of selection bias cannot be excluded.

4.1.4.2 Measurement Bias

Measurement bias occurs when the individual measurements or classifications of disease or exposure are inaccurate. There are several sources of measurement bias and their effects have varying importance (97).

Information bias refers to bias that arises from measurement errors and can be defined as a systematic error in collecting information from study subjects (97). In this study, interviewer-administered questionnaires were used. Compared to self-reported questionnaires, interviewer-guided questionnaires usually provide higher response rates and more complete answers. However, the subjects' answers may have been influenced by the interviewers. Asking questions in different ways or interpreting or coding information differently may result in information bias (104). In this study, in order to minimize this type of bias, all members of the research team and field workers were trained before the start of the data collection with regard to filling in the questionnaires. In addition, it was checked twice during the study period whether the data entries were been done according to protocol. Since the field workers and research assistants were from the local community, they knew the local

language and had a good understanding of the cultural norms. If a question was not answered, a variable would present missing values in the final analysis.

Although recall bias (differential recall of information by subjects with or without a disease of interest) is more important in retrospective case control studies, it may also have happened in this cross-sectional study (97). For instance, information about family history of disease, dietary habits, use of medications, etc, may have presented some deviations. Furthermore, the possibility of reporting bias cannot be excluded. Reporting bias, defined as selective revealing or suppression of information (97), may have occurred for example when questions about past medical history, alcohol consumption, smoking habits and monthly income were made. It is also noteworthy to consider the possibility of recall and reporting bias in the assessment of depression by the MADRS and HDRS. When assessing depression, some items of the scales may be subject to differential recall by the participants. Moreover, several sensitive questions need to be asked (e.g., questions about suicidal thoughts or attempts, genital disturbances, hypochondriacal delusions, etc), and some people may have concealed the truth due to religious or cultural reasons.

Concerning the anthropometric, blood pressure and body fat percentage measurements, only one team member performed the assessments after proper training. Everyday the weighing machine was calibrated against a standard (15Kg). The automatic electronic sphygmomanometer used was properly validated, checked and calibrated before the start of the data collection. However, it is acknowledged that electronic sphygmomanometers may produce systematic errors in some patients (105). Thus, the blood pressure measurements were taken twice in order to minimize any potential errors. All blood analyses were performed in a certified laboratory. Additionally, since misclassification errors can occur when estimating LDL-C levels by the Friedewald formula (95), those with triglyceride concentration exceeding 400mg/dl were not taken into account. They were considered as missing values.

4.1.5 Confounding

The term "confounding" comes from the Latin *confundere*, and means "to mix together". In a study of the association between exposure to a cause (or risk factor) and the occurrence of a disease, confounding can arise when another exposure exists in the study population and is associated both with the disease and the exposure being investigated. Thus confounding may take place when the effects of two exposures (risk factors) have not been

separated and the analysis concludes that the effect is due to one variable rather than the other. The influence of confounding factors can be quite substantial, and may even change the apparent direction of an association. For instance, a variable that seems to be protective may, after control of confounding, be actually harmful (97).

Since the problem may occur if this extraneous factor is unequally distributed between the exposure subgroups, the subjects were randomly selected to participate in this study. Additionally, the effect of age and gender was minimized by stratifying some of the analyses. Moreover, the most common confounding variables, which have been identified in the literature to influence the occurrence and association of diabetes and depression, were assessed and analyzed simultaneously by using multivariate statistical modeling. However, it must be acknowledged that some confounders might have not been controlled for.

4.1.6 Internal Validity

Internal validity can be described as the degree to which the results of an observation are correct for the particular population under study. Internal validity can be threatened by all sources of systematic error but can be increased by appropriate design and attention to detail (97). In order to secure internal validity, important strategies were applied to reduce the confounding effects and measurement bias as described above.

4.1.7 External Validity

External validity or generalizability is the extent to which the results of a study can be applied to other situations and other people (97). As mentioned previously, Brazil is a continental country with huge socioeconomic, ethnic and regional disparities. Therefore the findings in the present study may not be representative for the whole country. Caution should be taken when making generalizations of the results. Besides the city chosen to be the study site is located in a semi-urban area. Thus the prevalence of diabetes and depression might have been overestimated compared to rural areas and underestimated in relation to urban areas. However, it is relevant to state that the sample studied is still valid to compare gender differences and identify risk indicators for diabetes and depression in northeastern Brazil. Furthermore, this research can be used for national references and provide the basis for further studies to investigate whether the present findings are replicable in other regions of Brazil.

4.1.8 Strengths of the Study

This is the first population-based study about the relationship between diabetes and depression conducted in Brazil that included adults of all ages, both genders, and did not use self-reported data on diabetes. As described above, a reasonably large sample from the general population was randomly selected to participate in this study (an effort was made to keep the selection procedures of the subjects as random as possible). Thus the final sample was large enough to meet the required sample size for analysis. Additionally, since the participation rate in the study was high, it is less likely that non-respondent biases have taken place in the analysis.

As mentioned before, anthropometric parameters and body fat percentage were measured by one well-trained investigator. A validated automatic electronic sphygmomanometer was used to take blood pressure measurements, and the mean value of two measurements was used for analysis. Socio-demographic, economic and physical activity data were collected by one research assistant that was adequately trained before the start of the study. Pretesting of the questionnaires was also undertaken.

Depression was assessed by two rating scales and the agreement between them could be evaluated. The MADRS was conducted by a nurse with a long experience in the management of mental health patients, while the HDRS was performed by a general physician also skilled in the area (principal investigator). Both of them assessed depressive symptoms after proper training under the supervision of an experienced psychiatrist (Professor Fábio Gomes de Matos e Souza, local supervisor). All measures of depression were undertaken between the first (fasting sample) and second (2-hour post glucose load) blood drawings. The measurement of capillary HbA1c was only performed after the depression assessments. Since the results for the test of diabetes were not ready by the time the assessments of depression were complete, it is unlikely that those results influenced the depression scores.

Additionally, most potential confounding factors described in the literature about the topic of interest (age, gender, BMI, WHR, physical activity, smoking, etc) were carefully controlled in the multivariate regression models.

4.1.9 Limitations of the Study

The study was based on a cross-sectional design which cannot proove causal relationship between exposure and outcome as discussed previously. Despite random selection procedures, the samples were collected from one semi-urban area in the Northeast region of Brazil. Therefore the results ought to be interpreted with caution with respect to generalization to the whole country. However, since similar results have been found in studies in other populations (strong association between diabetes and depression), the external validity of this study is supported.

It is also noteworthy to state that this study has assessed symptoms of depression, rather than depression itself. Therefore the data cannot provide a true prevalence of depression *per se*. Additionally, the MADRS and HDRS do not differentiate between types of depression, or between unipolar and bipolar depression. Moreover, no interrater reliability tests were performed for the study population. However, previous studies have shown high levels of reliability for both the MADRS and HDRS in Brazil and other parts of the world (101). Moreover, we have examined the agreement between both scales (MADRS and HDRS) which was found to be excellent (Kappa = 0.913).

4.2 DISCUSSION OF THE MAIN RESULTS

4.2.1 Diabetes

In the present study, the overall prevalence rates of DM, IFG and IGT were 16.0%, 5.8% and 11.8% respectively. The prevalence of IGT and DM were higher than in any previous large studies in Brazil, while the prevalence of IFG showed more similar results (22, 23, 106). Additionally, in comparison with surveys in other countries in the Americas that used the WHO criteria, the prevalence of DM in this study showed similar results to those found in the United States, Jamaica, Mexico, Bolivia and Trinidad and Tobago (107). In the United States, the National Health and Nutrition Examination Survey (NHANES III, 1988-1994) observed a prevalence of DM of 14.3% in subjects aged 40-74 years (108). As mentioned previously, the Brazilian Multicenter Study (the first population-based survey in Brazil that used the WHO criteria for the diagnosis of diabetes, and the only one using a representative sample of the urban Brazilian population until now), conducted among 21,847 individuals aged 30-69 years from 1986 to 1988, found that the overall rates were 7.6 and 7.8%

for diabetes and IGT, respectively (22). Another population-based, cross-sectional study conducted in Minas Gerais, Brazil in 1997 (simple probabilistic sample of 816 adults aged 18-59 years) showed that the prevalence of DM and IFG were 2.33% and 5.64% respectively (106). On the other hand, a survey conducted in Ribeirão Preto, Brazil between 1996 and 1997 (random sample of 1,473 individuals aged 30-69 years) showed that the prevalence of DM and IGT (according to the WHO criteria) were 12.1% and 7.7% respectively (23).

As described previously, the prevalence of DM has been increasing throughout the world, especially in developing countries that have been undergoing a rapid industrialization and urbanization like Brazil. This increase has been related to lifestyle changes that have resulted in overweight, obesity, and decreased physical activity levels (107). This phenomenon may explain the elevated prevalence of DM found in Pindoretama, since this city has experienced growing urbanization and modernization over the past years. Corroborating such a relationship, among the previous studies conducted in Brazil, the prevalence of DM found in Ribeirão Preto (city that has also experienced environmental and lifestyle changes) was the closest to our results (23). It has been shown that post-prandial glucose concentrations are more determined by glucose uptake in insulin-sensitive tissues and are therefore more likely to be influenced by insulin resistance (109). On the other hand, it has been observed that β-cell dysfunction is significantly higher in IFG than IGT (110). Thus, the higher prevalence of IGT and similar rates of IFG in our study in relation to other surveys conducted many years back in Brazil support the hypothesis that lifestyle changes have led to higher levels of obesity, insulin resistance and occurrence of IGT and DM.

As observed in many other studies in Brazil and throughout the world, in our study, the prevalence of diabetes increased significantly with higher age and BMI, lower levels of physical activity and education, as well as among those with a family history of diabetes and higher WHR (22-24).

In the Brazilian Multicenter Study, age was an important indicator for the occurrence of DM, with a prevalence of 17.4% in the 60-69 year-old group (22). Another study from Rio de Janeiro, Brazil, age was also a relevant factor and the prevalence of DM was 22.4% among the women of this same age group (111). In our study, although the occurrence of diabetes increased significantly among older subjects (among those aged $\geq$ 51 years, the diabetes prevalence was 24.8%), age did not remain a significant indicator of diabetes in multivariate analysis. Similarly to age, lower level of physical activity was not independently

associated with diabetes. This can possibly be explained because almost 70% of the study population had sedentary lifestyles. In contrast, family history of DM, BF% and WHR, level of education, triglycerides and DBP were found to be strong risk indicators of DM, since they were independently associated with diabetes in multivariate analysis.

In our study, no significant difference was found between the different ethnic groups with regard to the prevalence rates of DM, IFG and IGT. Our results are in agreement with what was observed in the study from Ribeirão Preto, as well as in the Brazilian Multicenter Study (22, 23). In contrast, in the United States, the prevalence of DM among non-Hispanic blacks and Mexican-Americans was 1.6 to 1.9 times higher than among non-Hispanic whites (112). However, as described previously, it is likely that the extensive miscegenation of the overall Brazilian population may have reduced the differences among the ethnic groups.

As stated above, level of education was also found to be an important indicator of diabetes. Again, our findings are similar to those from the study conducted in Ribeirão Preto, since they observed that the prevalence of DM was 2.0 times higher among subjects with only basic education. One possible explanation may be the increased occurrence of other risk indicators in the population of lower education level. For instance, in Ribeirão Preto, the prevalence of obesity evaluated in the same population was higher among people of lower educational level (23). In this study, those who were illiterate had a significantly greater proportion of high WHR compared to those who had an education level of high school or higher (78.9% vs. 51.9%).

Although BMI was an important indicator in univariate analysis, it did not remain significantly associated with diabetes in multivariate analysis. For epidemiological studies, the body mass index has been regarded as a suitable indicator for overweight and obesity. Although it has been shown in many studies that high levels of BMI are related to increased morbidity and mortality, from the physiological point of view, it is not the degree of excess weight (as measured by the BMI) but the degree of body fatness that is important as a risk indicator. Additionally, accumulating evidence has suggested that the relationship between BMI and BF% may be different between ethnic groups (113, 114). Possibly because of differences in body build, energy intake or physical activity, the BMI cut-off values for overweight and obesity recommended by the WHO may not correspond to the same degree of fatness across different populations (115). Furthermore, in addition to the degree of obesity, some studies have shown that diabetic subjects present the android (upper body, male)

adipose tissue distribution more often than the gynoid (lower body, female) type of fat distribution (116). Kissebah et al. have observed that obese women without overt clinical symptoms of DM are more likely to have IGT and hyperinsulinemia, if their excessive fat mass is predominantly distributed above the waist (upper body obesity) than if the fat mass is mostly over the hips, thighs, and buttocks (lower body obesity) (117). In our study, BF% and WHR were independently associated with DM, indicating that, in this population, the degree of body fatness (BF%) and the abdominal adipose tissue distribution (WHR) were probably stronger indicators of diabetes than the total body fat mass (BMI) (115). Moreover, in line with the literature, in addition to central obesity and hyperglycemia, our study has also found that hypertension and dyslipidemia (all components of the metabolic syndrome) are independent risk indicators for T2DM (24).

4.2.2 Depression

In this study, we found that depressive symptoms were highly prevalent. Following MADRS, the prevalence of depression was 15.0%, while according to HDRS, the prevalence was 15.5%. In comparison with other community surveys that have used clinically defined case finding methods, our results are in line with what has been observed in countries like the United States and England (59).

As stated previously, population-based studies of psychiatric morbidity in Latin America and Brazil are rare. Many studies have been conducted in primary health care settings, or for specific populations, not allowing estimations of population rates. One of the reasons for this paucity of community-based surveys in Brazil is that the country is very large, with a diversity of cultural and socioeconomic aspects. Thus, it is difficult to make comparisons and deeper analyses about the burden of depression in the Brazilian population. One of the very few community surveys carried out in Brazil was a two-stage cross-sectional study conducted in 1997 in three metropolitan areas (Brasília, São Paulo and Porto Alegre). A 44-item screening instrument designed to assess psychiatric morbidity in adults in Brazilian urban areas was initially applied. Then, sub-samples of probable cases and non-cases (n=836) were interviewed by psychiatrists using the DSM-III Symptom Checklist. In that study, depression showed great variation between areas: from less than 3% (São Paulo and Brasilia) to 10% (Porto Alegre). As described by the authors, the great difference in the prevalence of depression in these three research sites might have occurred due to methodological problems,

such as low stability of the screening instrument and the distinct sampling designs, which might have biased the comparability of the data (53). Another community survey conducted in São Paulo, Brazil (including 1,464 residents aged 18 years or older) in 2002 reported that 16.8% of the subjects had at least one lifetime diagnosis of depressive episode, 7.1% in the year, and 4.5% in the month prior to interview. The instrument used was the Brazilian version of the Composite International Diagnostic Interview (CIDI), version 1.1, which provides lifetime, 12-month, and 1-month prevalence estimates for ICD-10 diagnoses (54). In our study, the prevalence rates found were higher than most of the figures observed in those previous studies conducted in Brazil. In both studies mentioned, the instruments used to assess depression were different from the scales applied here. Additionally, compared to those cities in which the other studies were conducted, the northeastern region of Brazil and more specifically our study site present lower socio-economic status, higher unemployment rates, lower level of education and worse health indicators. The above mentioned factors may explain the higher prevalence of depression in our study. Furthermore, longitudinal studies conducted elsewhere have shown that there is an increase in the prevalence of depression over time (51). Since the previous studies from Brazil have been conducted many years ago, it is also possible that an increase in the risk of depression has taken place over the recent years.

Following both the MADRS and HDRS, the prevalence of depression decreased significantly with higher BMI, although slight insignificant increase was observed for the group with obesity. Studies about the association between obesity and depression have shown conflicting results. Some have found a positive association, some a negative association and some no association at all (118). In a study conducted in Bangladesh among 1,271 subjects, also using the MADRS to assess depression, overweight individuals had fewer depressive symptoms than normal weight subjects (119). On the other hand, a study from the Netherlands among a sample of 43,534 individuals has found a very significant U-shaped association between BMI categories (underweight, normal, overweight and obesity) and depression (118). In our study, it is more likely that BMI and depression present a u-shaped association, even though our findings are far from conclusive. It is possible that if we had a larger sample size, we could have found a clearer picture regarding this issue. In addition, interestingly, in univariate analysis, depression following both scales was associated with higher BF%. However, in multivariate analysis, this association did not remain significant.

In multivariate analysis, the significant risk indicators of depression following both scales were gender, smoking habits and family history of depression. The prevalence of depressive symptoms was higher among females compared to males, as reported in many other studies from Brazil and other parts of the world (52, 55, 59). In our study, following the MADRS and HDRS, those who were current smokers were around 2.5 and 2.0 times more likely to have depressive symptoms, respectively. These results are in agreement with many other studies, since a strong association between smoking and depression has been found consistently (59, 120). Furthermore, numerous studies have shown that a positive family history of depression is associated with an increased risk of depression, which is also in line with our findings (61).

As described before, major depressive disorder has been associated with altered activity of the HPA axis. This abnormality has been demonstrated by an increase in plasma, urine, or cerebrospinal fluid levels of cortisol or by nonsuppression of cortisol in response to dexamethasone (the dexamethasone suppression test) (121-123). However, in our study, we did not observe a significant difference with regard to fasting plasma cortisol between depressed and non-depressed individuals. In a study conducted in the United States, a group of endogenously depressed patients evaluated over 24 hours was reported to hypersecrete cortisol primarily in the afternoon and evening hours. These findings suggested that the mean cortisol levels between 1 and 4 pm were a reliable and convenient indication of cortisol secretion, powerfully discriminating between cortisol hypersecretors and normosecretors (121). In a recent meta-analysis, clinically depressed and non-depressed individuals exhibited similar baseline and stress cortisol levels, but depressed patients had much higher cortisol levels during the recovery period. There was also a significant time of day effect in which afternoon studies were more likely to reveal higher baseline cortisol levels, blunted stress reactivity, and impaired recovery in depressed patients (124). Since in our study we evaluated only morning cortisol levels, it is possible that we could not find any significant difference between depressed and non-depressed subjects due to the time of the day in which the analysis was performed. Additionally, it has been found that melancholic depressed patients present increased HPA axis activity, whereas non-melancholic depressed patients show normal HPA axis activity (125). Thus, we cannot rule out the possibility that, in our study population, the depressed group might have been primarily composed by non-melancholic depressed patients, without significantly increased levels of cortisol. It is also noteworthy to mention that, given the scarce number of population-based studies on depression in Brazil,

the cut-off point that most correlates with depression in the Brazilian population is unknown. Thus it is also likely that the cut-off points applied in our study might have not been adequate, masking our ability to find an association between cortisol categories and depression. Moreover, the analysis of plasma cortisol levels provides a measure of the total cortisol, unbound and bound. Thus such an assessment may be affected by factors that influence corticosteroid-binding globulin (CBG) levels. Other measures of cortisol levels have been found to present a higher sensitivity and specificity such as twenty-four-hour urinary free cortisol (using high-performance liquid chromatography) (126). However, since this test is more expensive and troublesome, we could not apply it in our study.

4.2.3 Relationship between Diabetes and Depression

In this study, we found that depression (measured by MADRS and HDRS) was the second strongest indicator for the occurrence of diabetes after controlling for potential confounding fators. The risk for developing diabetes was about 4 times higher among depressed subjects. On the other hand, diabetes was the strongest independent risk indicator for the occurrence of depression in multivariate analysis following HDRS and the second strongest indicator according to MADRS. The risk for developing depression was approximately 3 and 3.5 times higher among individuals with diabetes following MADRS and HDRS, respectively. These findings are in line with other several studies conducted in different countries around the world (80, 83, 127, 128).

A recent study conducted in the United States among 1,665 elderly diabetic patients did not find a significant relationship between depression and hyperglycemia (129). This may have occurred because this study included only subjects older than 55 years of age, with pre-existing diabetes, and used a self-report measure of depression. Furthermore, since there was a high drop-out rate, we cannot rule out the possibility that a greater percentage of subjects lost to follow-up were depressed, which might have biased the results. Besides, older age is known to be associated with all chronic conditions. Therefore, the apparent lack of association between diabetes and depression may have been diluted in this older population with uncertain estimates of depression.

As described previously, studies about the relationship between diabetes and depression in Brazil are scarce, and most of them have been conducted in specialized diabetic

centers and included a small sample size. To the best of our knowledge, only one representative community survey conducted in Brazil on the comorbidity of diabetes and depression has been published so far. This cross-sectional study, carried out in the South region of Brazil among individuals aged 60 years and over (n=6,963), has observed that the burden of comorbid depression/diabetes appears to be comparable to that found in higher income countries. The comorbidity was present in 3.62% (52.5% beyond expectation). Depression without diabetes was reported by 17.3%, while diabetes without depression by 7.7%. Additionally, comorbid depression/diabetes was more likely in women and young elderly (aged 60-69 years) (87). In our study, following MADRS and HDRS, approximately 5.0% of the subjects had both diabetes and depression, around 10.0% had depression but not diabetes and 11.0% diabetes without depression. Furthermore, following MADRS, the subjects with both diabetes and depression were also more likely to be older and women. Thus, our results are in accordance with the findings from the South, since we have also observed a significant association between diabetes and depression. However, we have found a higher prevalence of those with both diabetes and depression, as well as a higher rate of diabetes without depression. In that survey, they used self-report data to identify the subjects with diabetes, which might have underestimated the true prevalence of DM. Additionally, the important socio-economic and cultural disparities between the South and Northeast regions may also explain part of the differences. Moreover, in our study, we included adults above 20 years of age, while the other survey included only individuals above 60 years. Thus, their higher rate of depression without diabetes (17.3% vs. 10.0%) might be in part due to the different age of the participants included.

CHAPTER 5

CONCLUSIONS AND IMPLICATIONS

5.1 IMPLICATIONS OF THE RESULTS

Research has established a link between depression and diabetes, even though the underlying mechanisms in this relationship are still debated. This thesis explored the relationship between depression and diabetes and implications for future studies related to the practice in the areas of screening, diagnosis, and management of depression in diabetic patients.

The association between diabetes and depression is not undisputed and warrants cross-cultural validity of the findings. Therefore the relationship between diabetes and depression should be studied in different cultures and set-ups. Information on this issue is scarce in Brazil and therefore the data presented in the thesis may serve as a reference for future studies.

Interventions for depression may be necessary in addition to lifestyle changes in order to prevent the expected substantial increase in the occurrence of type 2 diabetes. Our data may suggest exploring the effectivity of a simultaneous approach including psychiatric treatment in diabetes care for improved glycemic control in this population.

New public health policies of more effective depression screening programs and optimal management of depression and diabetes may be developed, and our data may serve as an important reference. However before undertaking such measures, a randomized clinical trial will be necessary to see the effect of simultaneous treatment of diabetes and depression for glycaemic control compared to those treated with only diabetes. Focused health promotion strategies for people with the double burden of diabetes and depression may reduce suffering and result in better quality of life.

5.2 CONCLUSIONS AND RECOMMENDATIONS

We found a high prevalence of both diabetes and depression in Northeastern Brazil. Diabetes was a strong independent risk indicator for the occurrence of depressive symptoms. An inverse significant association between symptoms of depression and the risk for developing diabetes was also observed. Given the socio-economic and cultural disparities in Brazil, these results should be further tested in other regions of the country in order to be confirmed. The directional nature and underlying pathophysiological mechanisms of this

relationship are still unclear and also warrant further research. Randomized controlled trials are needed to determine the effects of depression treatment on glycemic control and the long term course of diabetes.

Since comorbid depression in diabetes has been associated with poorer health outcomes and higher health care costs, clinical awareness and treatment options targeted toward these comorbid conditions should be emphasized. Health professionals who treat people with depression and/or diabetes should pay more attention to the recognition of this comorbidity.

Our data suggest that mental health should be included in diabetes prevention programs. Primary care providers are often responsible for managing these conditions and are well positioned to provide integrated care improving patients' physical and mental health outcomes. All diabetic patients should be routinely screened for depression. Management of these concomitant conditions should use a comprehensive approach that may include medication or referral for psychotherapy.

5.3 FULTURE RESEARCH

- We need large scale prospective studies to identify the direction of the relationship between diabetes and depression.
- Studies should be applied in different cultures and set-ups.
- Brazil is a multicultural and multiethnic country and therefore we need to conduct studies in different parts of the country with identical approach.
- Further studies are needed to confirm with a randomized clinical trial the effect of simultaneous treatment of diabetes and depression for glycaemic control compared to those treated with only diabetes.

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APPENDICES

Questionnaire - General Information, Socio-Demographic, Economic and Medical Data

ID Number: **Date:**

Interviewer:

1. Gender: …….
   (Male = 1, Female = 2)
2. Age: ……..
3. Place of birth: ……..
4. Race: ……
   (White = 1, Pardo (Brown) = 2, Black = 3, Yellow (i.e. East Asian) = 4, Indigenous = 5, Other = 6)
5. Religion: …….
   (Catholicism = 1, Protestantism = 2, Kardecist Spiritism = 3, Afro-Brazilian Religions = 4, Other Religion = 5, No Religion = 6)
6. Marital Status: …….
   (Married = 1, Single = 2, Divorced / Separated = 3, Cohabitant = 4, Widow / er = 5, Other = 6)
7. Level of Education: .....
   (Illiterate = 1, Primary School = 2, High School = 3, University or Higher = 4)
8. Years of Education completed: .....
9. Occupation:
   a. Current Status: ……..
      (Unemployed = 1, Part Time = 2, Full Time = 3, Retired = 4, Sick Benefit = 5)
   b. In case of being currently at work → Type of Occupation: ……..
      (Student =1, Agriculture = 2, Industry and Services = 3, Domestic Labour = 4, Construction = 5, Other = 6)
10. What is your monthly income? …….
11. How many members are there in your family?
    A) > 18 years: ……. B) <18years: …….
12. Health
    a. What is your present state of health? ……..
       (Poor = 1, Not so Good =2, Good = 3, Very Good = 4)
    b. Do you have any of these illnesses or have you suffered from them in the past? Are you on treatment? How long? What type of treatment? Regularly?

	Has the Disease	Had the Disease	Age of Onset	On Treatment	How Long	Type of Treatment	Regular Treatment
Diabetes Type 1							
Diabetes Type 2							
Heart Disease							
Hypertension							

Stroke / TIA							
Depression							
Kidney Disorders							
Hepatic illnesses							

c. Are you in use of any medication for conditions not mentioned previously? ……
(Yes = 1, No = 2)
   - If Yes, which types? ……..

d. For females → Are you pregnant? ……. / Have you ever received a diagnosis of Gestational Diabetes Mellitus? ……..
(Yes =1, No = 2)

13. Family History
    a. Have your parents or any of your siblings suffered from the following illnesses?

	Mother		Age of Onset	Father		Age of Onset	Siblings		Age of Onset
	Yes	No		Yes	No		Yes	No	
Type 2 Diabetes									
Heart Disease									
Hypertension									
Stroke / TIA									
Depression									

14. Smoking
    a. Smoking History: ……..
    (Never = 0, Previous Mild = 1, Previous Heavy = 2, Current Mild = 3, Current Heavy = 4)
    b. If you smoke daily at the moment, what do you smoke?

	Yes	No
Cigarettes		
Cigars		
Other		

    c. If you have smoked before, how long is it since you stopped smoking? ……..
    d. If you smoke now, or have smoked before:
       - How many cigarettes do you or did you usually smoke daily? ……
       - How old were you when you started smoking? ……..
       - How many years altogether have you smoked? ……..

15. Food and Drink
    a. How often do you usually eat the following kinds of foods?

	Seldom / Never	1-3 times pr. month	1-3 times pr. week	4-6 times pr. week	Daily
Fruits					
Cooked Vegetables					
Raw Vegetables / Salad					
Meat (beef, pork, chicken, etc)					
Fish					
Eggs					
Cereals (bread, noodles, biscuits, cookies or any food made from rice, maize, wheat, etc)					
White Tubers and Roots (white potatoes, cassava, or foods made from roots)					
Legumes, Nuts and Seeds (beans, peas, lentils, nuts, seeds, etc)					
Chocolates / Sweets					

b. What kind of fat do you use usually?

	Dairy-Butter	Hard Margarine	Soft / Light Margarine	Oil	Do Not Use
On Bread					
For Cooking					

16. How Often?

	Seldom / Never	1-3 times pr. month	1-3 times pr. week	4-6 times pr. week	Daily
On Bread					
For Cooking					

a. How much do you usually drink of the following?

	Seldom / Never	1-6 glasses pr. wk	1 glass pr. day	2-3 glasses pr. day	4 glasses or more pr. day
Full Cream Milk, Yoghurt					
Semi-Skimmed Milk, Light Yoghurt					
Skimmed Milk (sour / sweet)					
Fruit Juice					
Water					
Coca-Cola, Pepsi Cola or suchlike					
Other “fizzy” drinks / Thirst Quenchers					

b. How many cups of tea or coffee do you drink daily?
   Number Cups Tea: ……..
   Number Cups Coffee: ……..
   - Do you take sugar with tea or coffee? ……
   (Yes = 1, No = 2)

c. How often have you consumed alcohol in the course of the past year? (Low alcohol beer and non alcoholic beer are not included)

Never	About once pr. mth	2-4 times pr. mth	ca. 2-3 times pr. wk	ca. 4 or more times pr. wk

To be filled by the Investigators

17. Fasting Blood Sample →Date and Time……
    Time of Last Meal……..
18. Glucose Drink →Time: …….
19. Anthropometrics
    Height (cm): …….. Weight (Kg): …… Hip circumference (cm): …….Waist circumference (cm): ……
20. Body Fat Percentage: .....
21. Blood pressure (SBP/DBP) → First measure: ……. Second Measure: ……..
22. Second Blood Sample →Time: …….
23. HbA1c: .....

International Physical Activity Questionnaire (IPAQ)

I am going to ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Now, think about all the *vigorous* activities which take *hard physical effort* that you did in the last 7 days. Vigorous activities make you breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities?

   _____ Days per week

   ( ) Don't Know/Not Sure

   ( ) Refused

   [**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time.]

   [**Interviewer note**: If respondent answers zero, refuses or does not know, skip to Question 3]

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   __ __ Hours per day
   __ __ __ Minutes per day

   ( ) Don't Know/Not Sure

   ( ) Refused

   [**Interviewer clarification**: Think only about those physical activities you do for at least 10 minutes at a time.]

   [**Interviewer probe**: An average time for one of the days on which you do vigorous activity is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, ask: "How much time in total would you spend **over the last 7 days** doing vigorous physical activities?"

   __ __ Hours per week
   __ __ __ __Minutes per week

   ( ) Don't Know/Not Sure

   ( ) Refused

Now think about activities which take *moderate physical effort* that you did in the last 7 days. Moderate physical activities make you breathe somewhat harder than normal and may

include carrying light loads, bicycling at a regular pace, or doubles tennis. Do not include walking. Again, think about only those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities?

____ Days per week

( ) Don't Know/Not Sure

( ) Refused

[**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time]

[**Interviewer Note**: *If respondent answers zero,* refuses or does not know, skip to Question 5]

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

__ __ Hours per day
__ __ __ Minutes per day

( ) Don't Know/Not Sure

( ) Refused

[**Interviewer clarification**: Think only about those physical activities that you do for at least 10 minutes at a time.]

[**Interviewer probe**: An average time for one of the days on which you do moderate activity is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, or includes time spent in multiple jobs, ask: "What is the total amount of time you spent over the **last 7 days** doing moderate physical activities?"

__ __ __ Hours per week
__ __ __ __Minutes per week

( ) Don't Know/Not Sure

( ) Refused

Now think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

____ Days per week

( ) Don't Know/Not Sure

( ) Refused

[**Interviewer clarification**: Think only about the walking that you do for at least 10 minutes at a time.]

[**Interviewer Note**: *If respondent answers zero*, refuses or does not know, skip to Question 7]

6. How much time did you usually spend **walking** on one of those days?

__ __ Hours per day
__ __ __ Minutes per day

( ) Don't Know/Not Sure

( ) Refused

[**Interviewer probe**: An average time for one of the days on which you walk is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, ask: "What is the total amount of time you spent walking over **the last 7 days**?"

__ __ __ Hours per week
__ __ __ __Minutes per week

( ) Don't Know/Not Sure

( ) Refused

Now think about the time you spent sitting on week days during the last 7 days. Include time spent at work, at home, while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.

7. During the last 7 days, how much time did you usually spend ***sitting*** on a **week day**?

__ __ Hours per weekday
__ __ __ Minutes per weekday

( ) Don't Know/Not Sure

( ) Refused

[**Interviewer clarification**: Include time spent lying down (awake) as well as

sitting]

[**Interviewer probe**: An average time per day spent sitting is being sought. If the respondent can't answer because the pattern of time spent varies widely from day to day, ask: "What is the total amount of time you spent *sitting* last **Wednesday**?"

__ __ Hours on Wednesday
__ __ __ Minutes on Wednesday

( ) Don't Know/Not Sure

( ) Refused

Montgomery-Åsberg Depression Rating Scale (MADRS)

1. APPARENT SADNESS - *Representing despondency, gloom and despair (more than just ordinary transient low spirits), reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.*
0 = No sadness.
1
2 = Looks dispirited but does brighten up without difficulty.
3
4 = Appears sad and unhappy most of the time.
5
6 = Looks miserable all the time. Extremely despondent.

2. REPORTED SADNESS - *Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.*
0 = Occasional sadness in keeping with the circumstances.
1
2 = Sad or low but brightens up without difficulty.
3
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 = Continuous or unvarying sadness, misery or despondency.

3. INNER TENSION - *Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.*
0 = Placid. Only fleeting inner tension.
1
2 = Occasional feelings of edginess and ill-defined discomfort.
3
4 = Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 = Unrelenting dread or anguish. Overwhelming panic.

4. REDUCED SLEEP - *Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.*
0 = Sleeps as usual.
1
2 = Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
3
4 = Sleep reduced or broken by at least two hours.
5
6 = Less than two or three hours sleep.

5. REDUCED APPETITE - *Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.*
0 = Normal or increased appetite.
1
2 = Slightly reduced appetite.
3
4 = No appetite. Food is tasteless.
5
6 = Needs persuasion to eat at all.

6. CONCENTRATION DIFFICULTIES - *Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.*
0 = No difficulties in concentrating.
1
2 = Occasional difficulties in collecting one's thoughts.
3
4 = Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 = Unable to read or converse without great difficulty.

7. LASSITUDE - *Representing difficulty in getting started or slowness in initiating and performing everyday activities.*
0 = Hardly any difficulties in getting started. No sluggishness.
1
2 = Difficulties in starting activities.
3
4 = Difficulties in starting simple routine activities, which are carried out with effort.
5
6 = Complete lassitude. Unable to do anything without help.

8. INABILITY TO FEEL - *Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.*
0 = Normal interest in the surroundings and in other people.
1
2 = Reduced ability to enjoy usual interests.
3
4 = Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5
6 = The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. PESSIMISTIC THOUGHTS - *Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.*
0 = No pessimistic thoughts.
1
2 = Fluctuating ideas of failure, self-reproach or self- depreciation.
3

4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 = Delusions of ruin, remorse and unredeemable sin. Self- accusations which are absurd and unshakable.

10. SUICIDAL THOUGHTS - Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.
0 = Enjoys life or takes it as it comes.
1
2 = Weary of life. Only fleeting suicidal thoughts.
3
4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Hamilton Depression Rating Scale (HDRS)

1. DEPRESSED MOOD *(sadness, hopeless, helpless, worthless)*
0 = Absent.
1 = These feeling states indicated only on questioning.
2 = These feeling states spontaneously reported verbally.
3 = Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
4 = Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2. FEELINGS OF GUILT
0 = Absent.
1 = Self reproach, feels he/she has let people down.
2 = Ideas of guilt or rumination over past errors or sinful deeds.
3 = Present illness is a punishment. Delusions of guilt.
4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3. SUICIDE
0 = Absent.
1 = Feels life is not worth living.
2 = Wishes he/she were dead or any thoughts of possible death to self.
3 = Ideas or gestures of suicide.
4 = Attempts at suicide (any serious attempt rates 4).

4. INSOMNIA: EARLY IN THE NIGHT
0 = No difficulty falling asleep.
1 = Complains of occasional difficulty falling asleep, i.e. more than 1⁄2 hour.
2 = Complains of nightly difficulty falling asleep.

5. INSOMNIA: MIDDLE OF THE NIGHT
0 = No difficulty.
1 = Patient complains of being restless and disturbed during the night.
2 = Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

6. INSOMNIA: EARLY HOURS OF THE MORNING
0 = No difficulty.
1 = Waking in early hours of the morning but goes back to sleep.
2 = Unable to fall asleep again if he/she gets out of bed.

7. WORK AND ACTIVITIES
0 = No difficulty.
1 = Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
2 = Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).

3 = Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
4 = Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8. RETARDATION *(slowness of thought and speech; impaired ability to concentrate; decreased motor activity)*
0 = Normal speech and thought.
1 = Slight retardation during the interview.
2 = Obvious retardation during the interview.
3 = Interview difficult.
4 = Complete stupor.

9. AGITATION
0 = None.
1 = Fidgetiness.
2 = Playing with hands, hair, etc.
3 = Moving about, can't sit still.
4 = Hand wringing, nail biting, hair-pulling, biting of lips.

10. ANXIETY PSYCHIC
0 = No difficulty.
1 = Subjective tension and irritability.
2 = Worrying about minor matters.
3 = Apprehensive attitude apparent in face or speech.
4 = Fears expressed without questioning.

11. ANXIETY SOMATIC *(physiological concomitants of anxiety, such as:* ***- Gastro-intestinal:*** *dry mouth, wind, indigestion, diarrhea, cramps, belching.* ***- Cardio-vascular:*** *palpitations, headaches.* ***– Respiratory:*** *hyperventilation, sighing.* ***- Urinary Frequency – Sweating****)*
0 = Absent.
1 = Mild.
2 = Moderate.
3 = Severe.
4 = Incapacitating.

12. SOMATIC SYMPTOMS GASTRO-INTESTINAL
0 = None.
1 = Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 = Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13. GENERAL SOMATIC SYMPTOMS
0 = None.
1 = Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
2 = Any clear-cut symptom rates 2.
14. GENITAL SYMPTOMS *(symptoms such as: loss of libido, menstrual disturbances)*

0 = Absent.
1 = Mild.
2 = Severe.

15. HYPOCHONDRIASIS
0 = Not present.
1 = Self-absorption (bodily).
2 = Preoccupation with health.
3 = Frequent complaints, requests for help, etc.
4 = Hypochondriacal delusions.

16. LOSS OF WEIGHT *(Rate either A or B)*
A) According to the patient:
0 = No weight loss.
1 = Probable weight loss associated with present illness.
2 = Definite (according to patient) weight loss.

OR

B) According to weekly measurements:
0 = Less than 1 lb (500 g), weight loss in week.
1 = Greater than 1lb (500 g), weight loss in week.
2 = Greater than 2 lb (1000 g), weight loss in week.

17. INSIGHT
0 = Acknowledges being depressed and ill.
1 = Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 = Denies being ill at all.

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:

Executive officer:	Phone number:	Our date:	Reference
Gjøril Bergva	22845529	01.06.2012	2012/779/REK sør-øst D
REC south-east		**Deres dato:** 24.04.2012	**Deres referanse:**

Att: Akhtar Hussain

2012/779 Depression and Diabetes in Brazil

In reference to your application reviewed by the Committee on the 10th of May 2012.

Chief Investigator: Akhtar Hussain
Institution responsible: University of Oslo

Project description
The main purpose of the study is to assess the prevalence of depression and diabetes, and its association in northeastern Brazil. By providing such information, the study ultimately aims to optimize prevention and health promotion strategies, patients' care and promote a more cost-effective allocation of resources.

Data comprise of blood pressure and anthropometric measurements, blood glucose and lipids levels, questionnaires (information on dietary habits; physical activity; use of medications; current or past history of some illnesses; smoking; alcohol consumption, occurrence of depression). The blood samples will be destroyed immediately after analysis.

About 580 persons will be randomly included, using the voter`s list of the city. Prior to the

survey, the selected persons will be contacted by community health workers, informing them of the study purpose and methods of investigation. The study is based on informed consent. In case of illiteracy, verbal consent will be sought.

The project will be considered by the local Medical Research Ethics Comitee in Brazil.

The Committee's evaluation of the project
The Committee reviewed the application during its meeting on 10 May 2012. The project was assessed in accordance to the Norwegian Research Ethics Act of 30 June 2006 and Act on medical and health research (the Health Research Act) of 20 June 2008 for the regional committees for medical and health research ethics.

The commitee has evaluated the project, and has no comments.

The Committee's decision
The project is approved.

The approval is valid until 31.12.2012. Data must be deleted after the prosject has ended.

The decision of the committee may be appealed to the National Committee for Research Ethics in Norway. The appeal should be sent to the Regional Committee for Research Ethics in Norway, South-East D. The

deadline for appeals is three weeks from the date on which you receive this letter.

Med vennlig hilsen

Stein A. Evensen
Professor dr. med.
Chair

Gjøril Bergva
Executive officer

Copy: line.low@medisin.uio.no; universitetsdirektor@uio.no